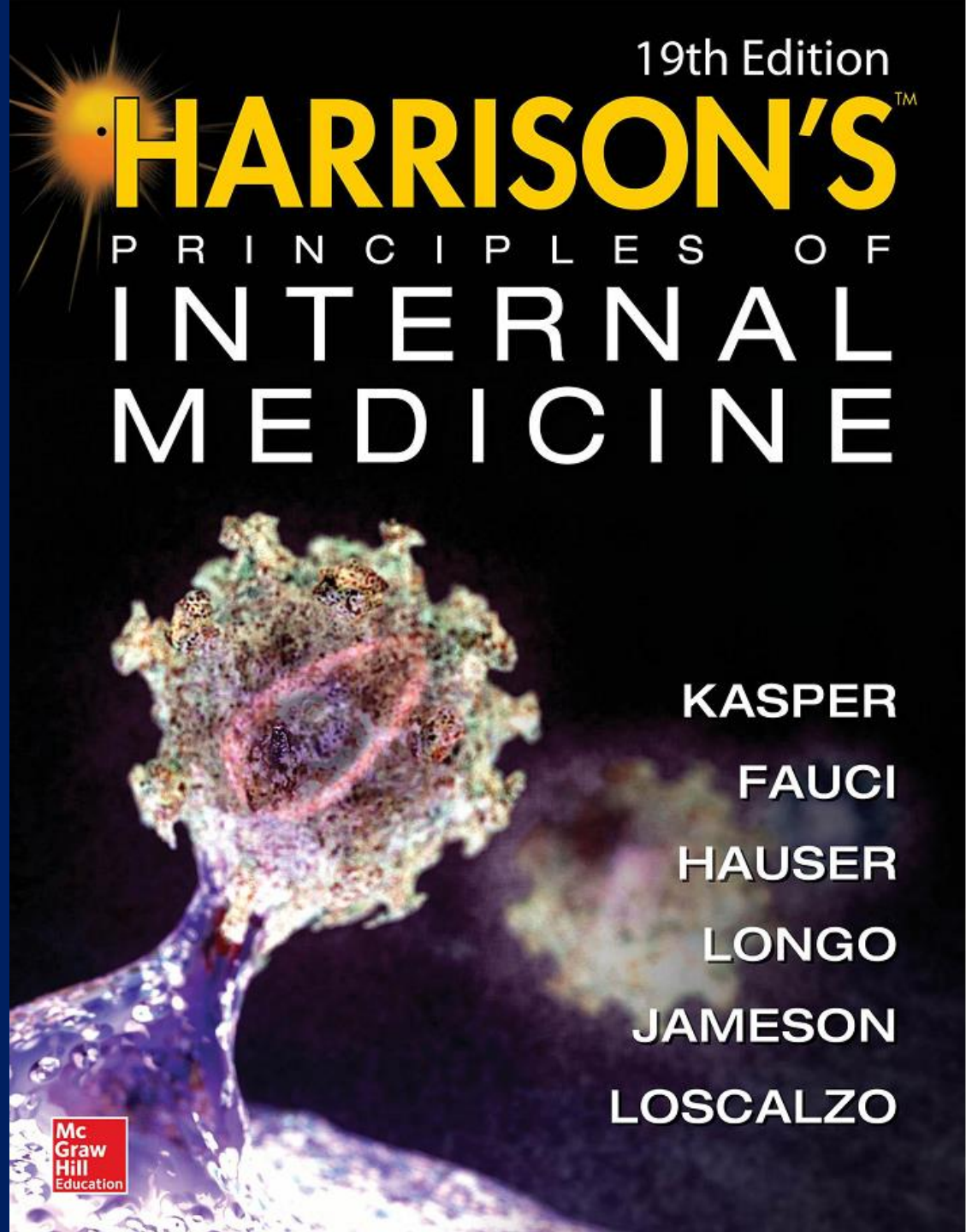
THE INTERSTITIAL LUNG DISEASES (ILDS)

DR.MEHDI FARZMEHDI

Interstitial Lung Diseases

INTERSTITIAL LUNG DISEASES 315

TALMADGE E. KING, JR

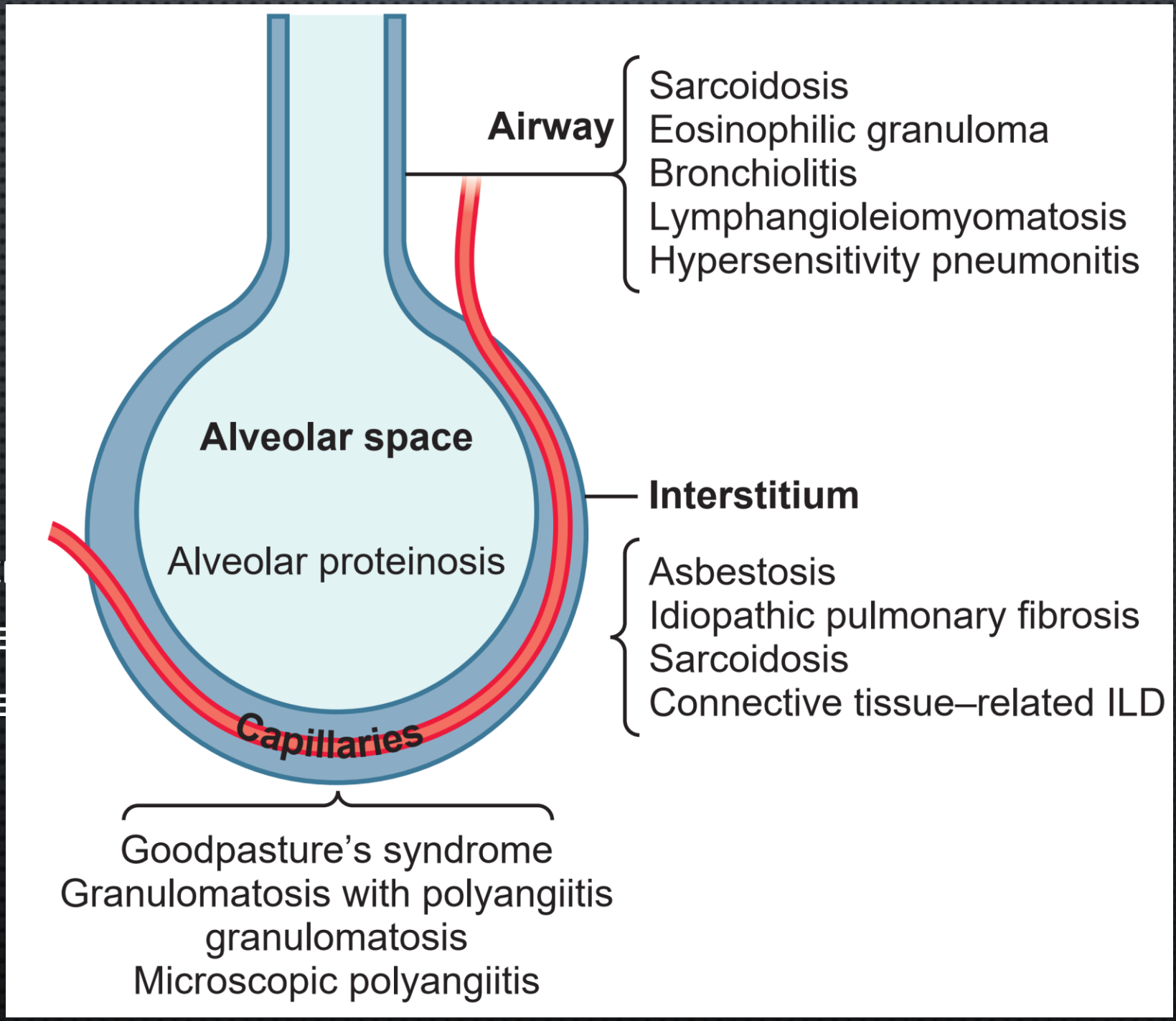


ILDs represent

- parenchyma of the lung
- alveolar epithelium
- capillary endothelium
- *spaces between those structures*
- *perivascular and lymphatic tissues*

Involve

- INTE
- BASE
- BASE



- inf
- Inf
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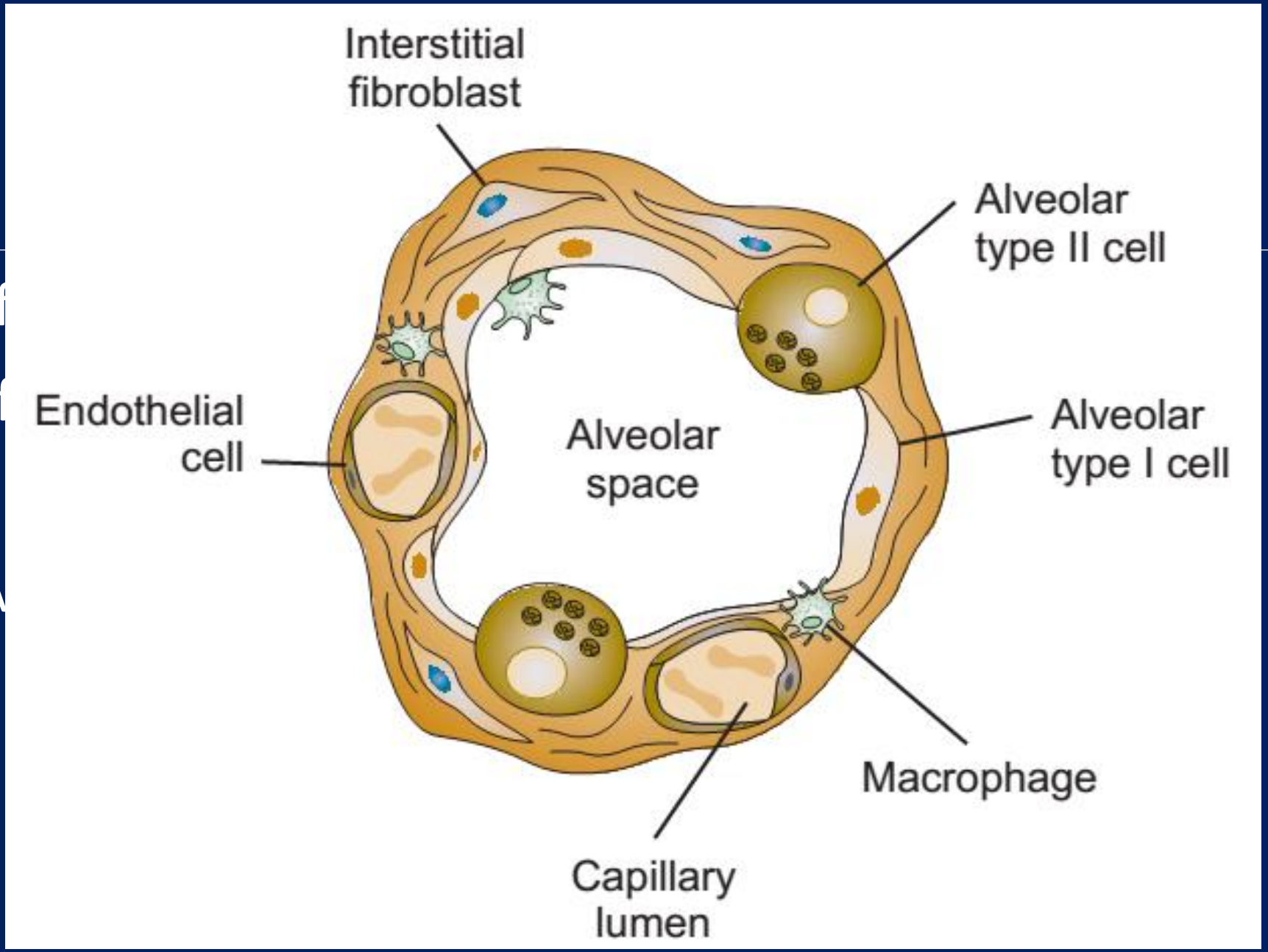
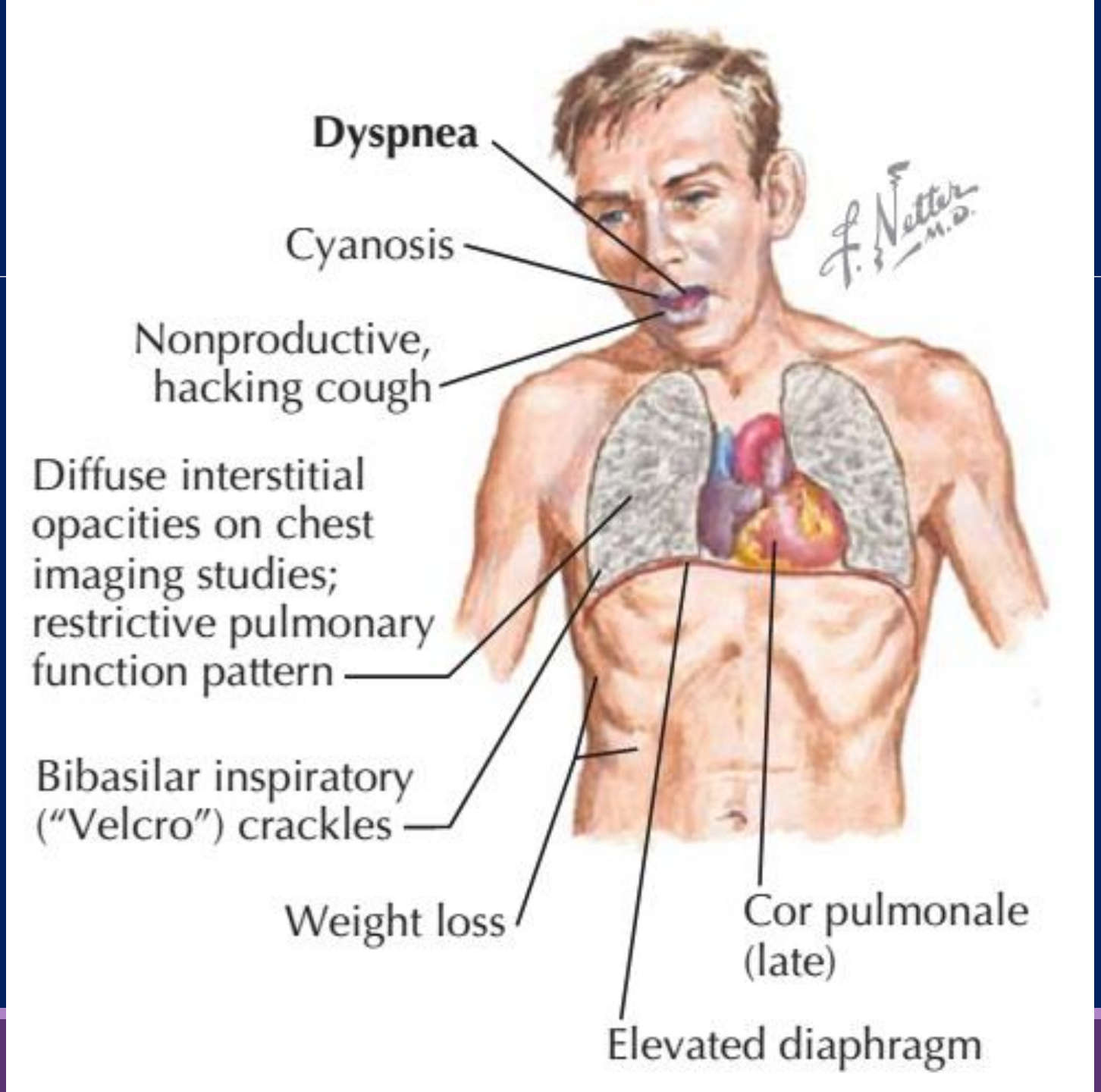


INTRODUCTION

- Fibroblastic proliferation
- Excessive collagen deposition

- histologic hallmarks of ILD


Dyspnea
Cyanosis
Nonproductive, hacking cough
Diffuse interstitial opacities on chest imaging studies; restrictive pulmonary function pattern
Bibasilar inspiratory ("Velcro") crackles
Weight loss
Elevated diaphragm
Cor pulmonale (late)
F. Netter M.D.

interstitial Lung Diseases

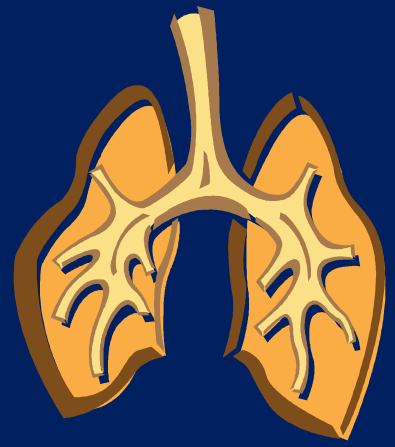
- ***progressive exertional dyspnea***
- ***persistent nonproductive cough***
- *Hemoptysis*
- *Wheezing*
- *Chest pain*
- **interstitial opacities on CXR**

Causes

Drugs

CTD

Sarcoidosis



Idiopathic

Inorganic
(Pneumoconiosis)

Organic

PATHOGENESIS ILDs

- nonmalignant
- not infectious agents
- injury to fibrosis is not known ?
- mechanisms of repair have common features

Inflammation and Fibrosis

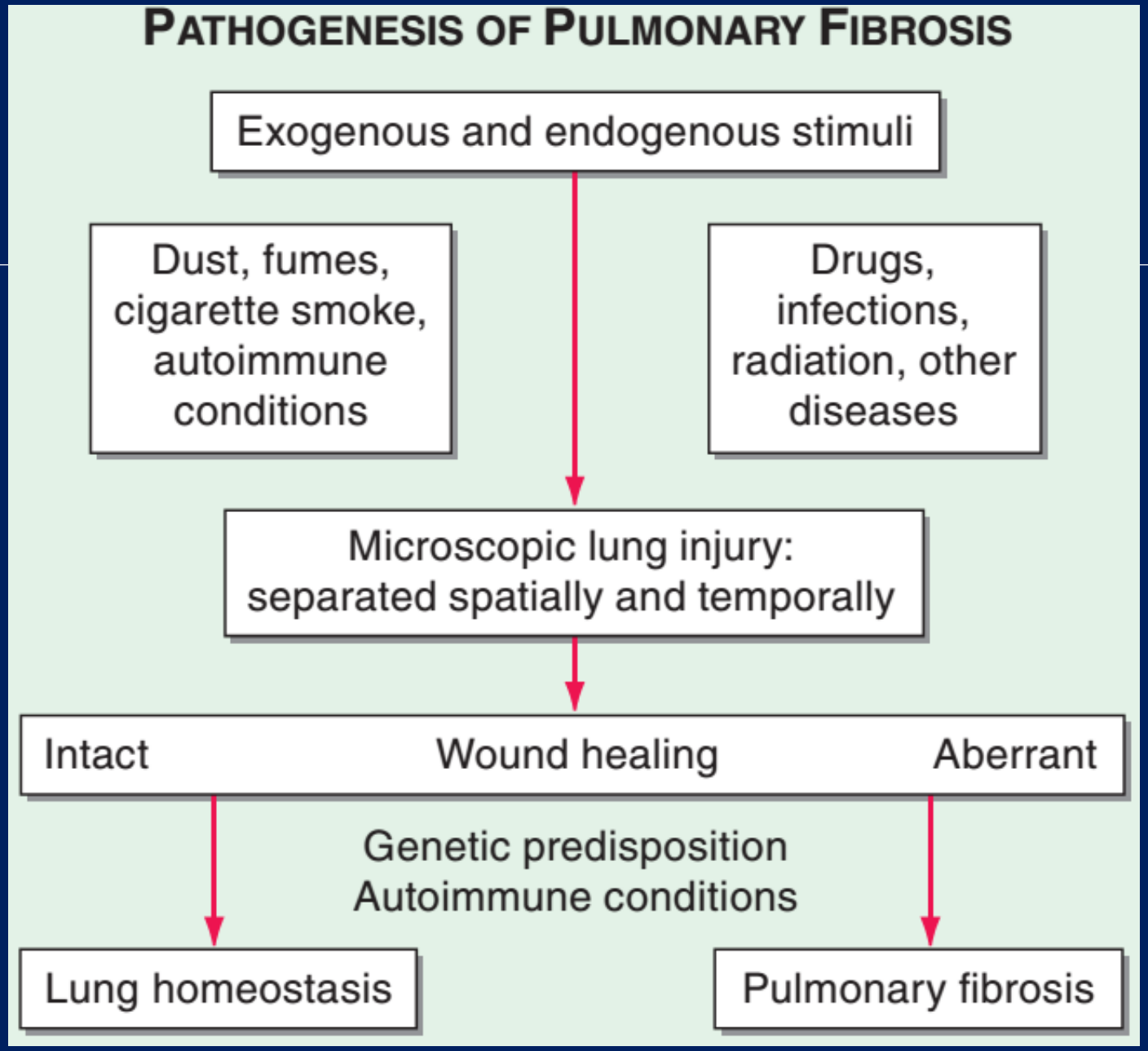
- inflammation in the air spaces and alveolar walls
- Chronic
- adjacent portions of the interstitium and vasculature

eventually causes

- interstitial fibrosis

ILD

- Irreversible scarring (fibrosis)
  - alveolar walls
  - Airways
  - vasculature
- often progressive
- ↓ ventilatory function and gas exchange


PATHOGENESIS OF PULMONARY FIBROSIS
Exogenous and endogenous stimuli
Dust, fumes, cigarette smoke, autoimmune conditions
Drugs, infections, radiation, other diseases
Microscopic lung injury: separated spatially and temporally
Intact
Wound healing
Aberrant
Genetic predisposition
Autoimmune conditions
Lung homeostasis
Pulmonary fibrosis

ILDs

- ***>200 known*** individual diseases
  - diffuse parenchymal lung involvement

- Idiopathic
- Multiorgan process, CTDs

IDIOPATHIC INTERSTITIAL PNEUMONIAS

- IPF
- NSIP
- RB-ILD
- DIP
- COP
- AIP
- Rare IIPs include
  - LIP
  - idiopathic pleuroparechymal fbroelastosis
- Unclassifable IIP

Histopathology

- predominant inflammation and fibrosis
- predominantly granulomatous reaction

Histopathology

- ***Alveolitis, Interstitial Inflammation, and Fibrosis***
  - Known Cause
  - Unknown Cause
- ***Granulomatous***
  - Known Cause
  - Unknown Cause

Histopathology

- ***Alveolitis, Interstitial Inflammation, and Fibrosis***
  - Known Cause
    - Asbestos
  - Unknown Cause
    - IPF
- ***Granulomatous***
  - Known Cause
    - HP
  - Unknown Cause
    - SARCOIDOSIS

CURRENT CLASSIFICATIONS

- **HISTOPATHOLOGY AND CLINICAL SYNDROMES**
  - IDIOPATHIC INTERSTITIAL PNEUMONITIDES
  - GRANULOMATOUS DISORDERS
  - CONNECTIVE TISSUE–RELATED ILDS
  - DRUG-INDUCED ILDS
  - PULMONARY VASCULITIC DISORDERS
  - UNKNOWN ORIGIN THAT EXHIBIT WELL-DEFINED SYNDROMES SUCH AS
    - PULMONARY LANGERHANS CELL HISTIOCYTOSIS (LCH)
    - LYMPHANGIOLEIOMYOMATOSIS

ILD

- *Acute phase*
- *Chronic phase*
- *Rarely, recurrent*

HISTORY
Duration of Illness

- **Acute presentation (days to weeks), unusual**
  - allergy (drugs, fungi, helminths)
  - acute interstitial pneumonia (AIP)
  - Hypersensitivity pneumonitis

confused with atypical pneumonias

DIAGNOSIS

- ***SOME ILDS MANIFEST IN AN ACUTE FASHION***
- ACUTE PNEUMONITIS DUE TO SYSTEMIC LUPUS ERYTHEMATOSUS
- ACUTE HYPERSENSITIVITY PNEUMONITIS (HP)
- SOME DRUG REACTIONS
- ACUTE INTERSTITIAL PNEUMONIA
- **INFECTION OFTEN NEEDS TO BE RULED OUT IN THESE CASES**

HISTORY
Duration of Illness

- **Subacute presentation (weeks to months)**
  - Sarcoidosis
  - drug-induced ILDs

HISTORY
Duration of Illness

- **chronic presentation (months to years)**
  - IPF
  - Sarcoidosis
  - PLCH
  - Pneumoconioses
  - CTDs

DIAGNOSIS

- DELAYED
- HRCT

DIAGNOSIS

- MOST ILDS
- IPF
- CHRONIC, PROGRESSIVE SYMPTOMS
-

age, race, and sex

- ***Most patients with IPF are older than 60 years***
- Sarcoidosis
- LAM
- PLCH

Ages of 20 and 40 years

Gender

- LAM / tuberous sclerosis → exclusively → **premenopausal women**
- CTDs → **women**
- ILD in RA
- Pneumoconioses

→ **men**

Smoking History usually current or former smokers

- Two-thirds to 75% → ***IPF*** and ***familial lung fibrosis***
- PLCH
- RB_ ILD
- DIP

DIAGNOSIS

- ***ENVIRONMENTAL EXPOSURES***
- EXPOSURE TO PET BIRDS OR HOT TUBS MAY SUGGEST HP
- ***OCCUPATIONAL HISTORY***
- PNEUMOCONIOSES → ASBESTOS AND SILICA EXPOSURE
- BERYLLIOSIS
- GRANULOMATOUS PNEUMONITIS IN INDOOR LIFEGUARDS EXPOSED TO MOLDS

Occupational History

- **hypersensitivity pneumonitis**
  - Pigeon breeder's disease & workplace (farmer's lung)
  - fever, chills, and an abnormal CXR
  - symptoms may reappear

Past History

- Parasitic infections
- Travel history

DIAGNOSIS

- ***THE HISTORY***
- RASH, DYSPHAGIA, ARTHRITIS, AND RAYNAUD'S PHENOMENON

- CONNECTIVE TISSUE DISORDER

DIAGNOSIS

- ***POORLY CONTROLLED ASTHMA***
- RADIOGRAPHIC INFILTRATES
- CONSTITUTIONAL SYMPTOMS
- ***CHURG-STRAUSS SYNDROME***

DIAGNOSIS

- ***SEVERE SINUS DISEASE***
- ***GRANULOMATOSIS WITH POLYANGIITIS GPA (WG)***

DIAGNOSIS

- ***DRUG-INDUCED ILD***

Diagnosis

- ***Clinician***
- ***Radiologist***
- ***Pathologist***

en

- HRC
- Tissu ung biopsy

physical examination

- oxygen desaturation with exertion in early ILD.
- decreased chest expansion during inspection.
- Auscultation Velcro-like crackles at the lung bases.
- clubbing.

PHYSICAL EXAMINATION

- **SKIN RASHES,**
- **ARTHRITIS WITH JOINT DEFORMITIES,**
- **RAYNAUD'S PHENOMENON,**
- **DYSPHAGIA**
- ***CONNECTIVE TISSUE–RELATED ILD SUCH AS***
  - DERMATOMYOSITIS OR POLYMYOSITIS,
  - PROGRESSIVE SYSTEMIC SCLEROSIS,
  - MIXED CONNECTIVE TISSUE DISORDER.

PHYSICAL EXAMINATION

- Evidence of right ventricular heart failure
- Jugular vein distention
- Cardiac gallop
- Loud P2 sound
- Leg edema

pulmonary hypertension

- Chronic hypoxemia and is often related to end-stage lung disease.

PHYSICAL EXAMINATION

- Tachypnea
- Bibasilar end-inspiratory dry crackles

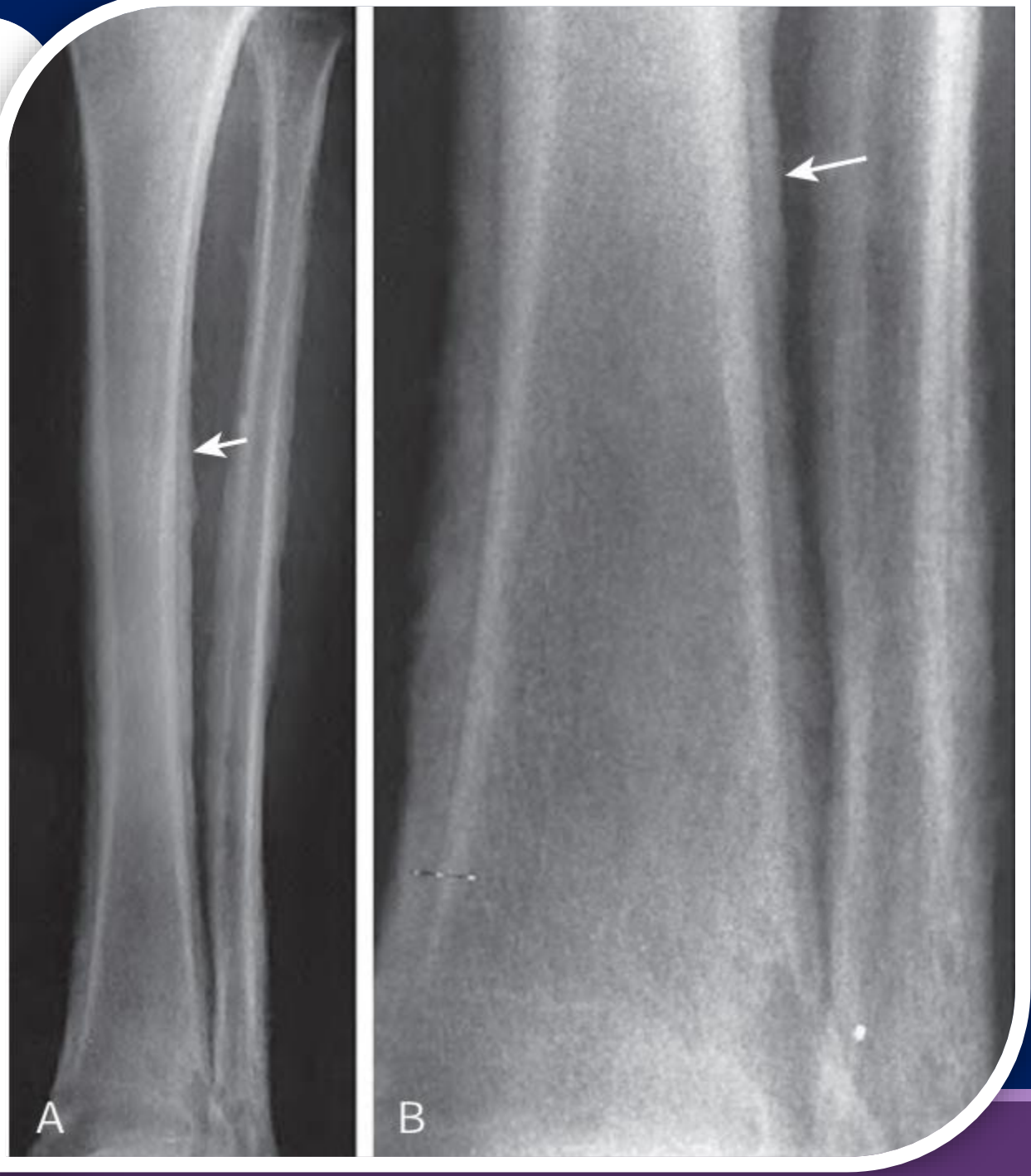
} *inflammation*

- **Scattered late inspiratory high-pitched rhonchi**
- **so-called inspiratory squeaks**
- **Bronchiolitis**
- **cardiac examination is usually normal**
- **Pulmonary hypertension and cor pulmonale**
- **Cyanosis and clubbing of the digits**

Normal angl
of nail b

Dist
of

Clubbed fingers



- EXAMINATION

Clubbing
Bibasal Crackles
Cor Pulmonale
Respiratory Effort ↑
Reduced Expansion
Cyanosis

Clinical Features

HISTORY

Onset?
Time?
Progressive?

After HPCx:

PMHx
Smoking
Pets
Exposure in Job/Hobby
Ask specific meds!
If confident ask CTD Sx

Dyspnea (Progressive)
Cough (No Sputum)
Ex Tolerance
Weight Loss
Fatigue

DIAGNOSIS

- ***LABORATORY STUDIES*** **EOSINOPHILIA**
- **PULMONARY INFLTRATES AND PERIPHERAL BLOOD EOSINOPHILIA**

CHEST RADIOGRAPH
UPPER- AND MID-LEVEL LUNG FIELDS

- SARCOIDOSIS,
- LCH
- LYMPHANGIOLEIOMYOMATOSIS

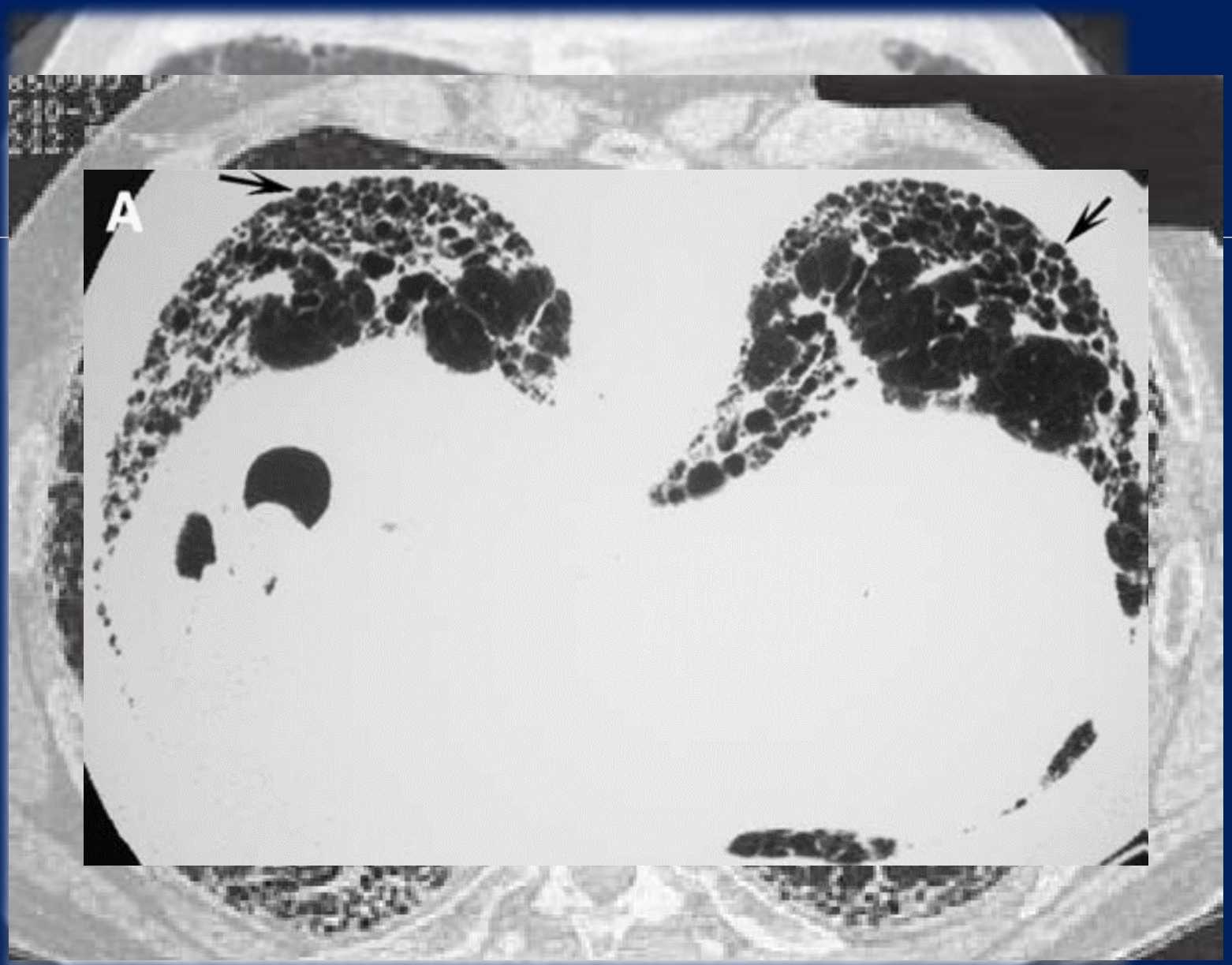
CHEST RADIOGRAPH
LOWER-LEVEL LUNG FIELDS

- IPF,
- ASBESTOSIS,
- MANY CONNECTIVE TISSUE–RELATED ILDS

CHEST IMAGING STUDIES
Chest X-Ray ILD

- ***Bibasilar reticular pattern***
  - A nodular
    - mixed pattern of alveolar filling and increased reticular
- ***Honeycombing***

- *CXR is nonspecific and usually does not allow a specific diagnosis*


A

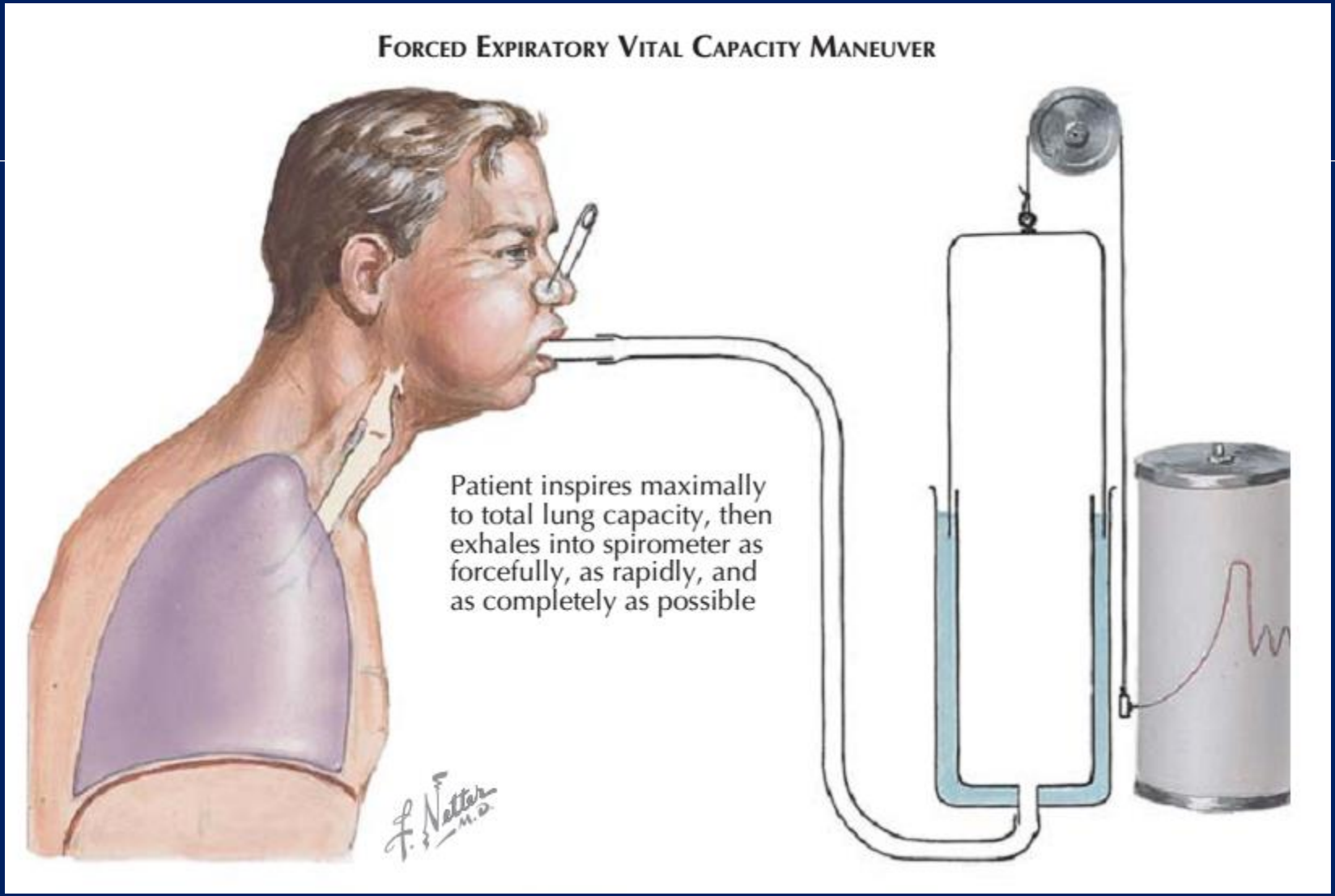
PULMONARY FUNCTION TESTING
Spirometry

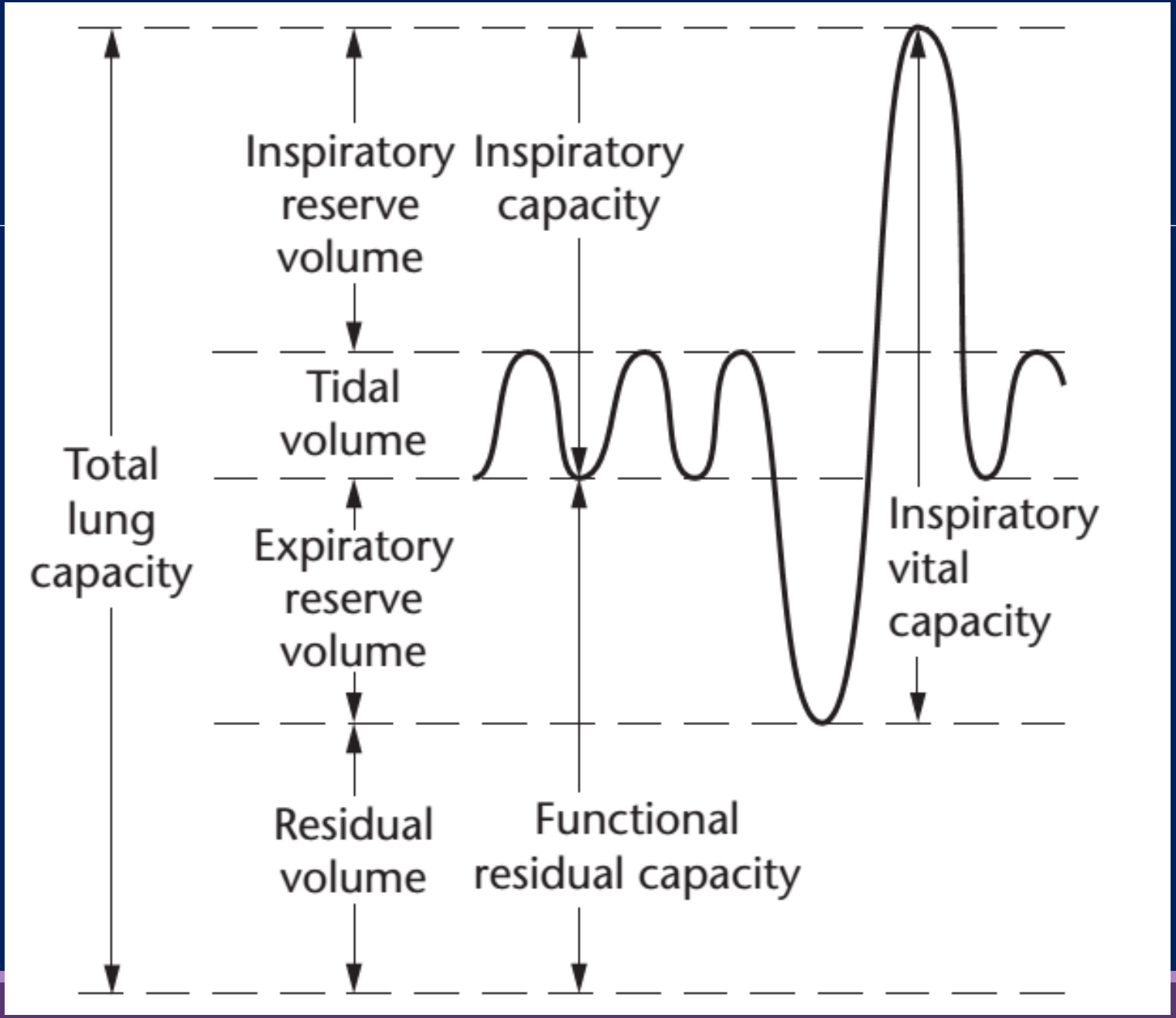
- Most forms of ILD produce a restrictive defect
- TLC
- FRC
- RV

PULMONARY FUNCTION TESTING

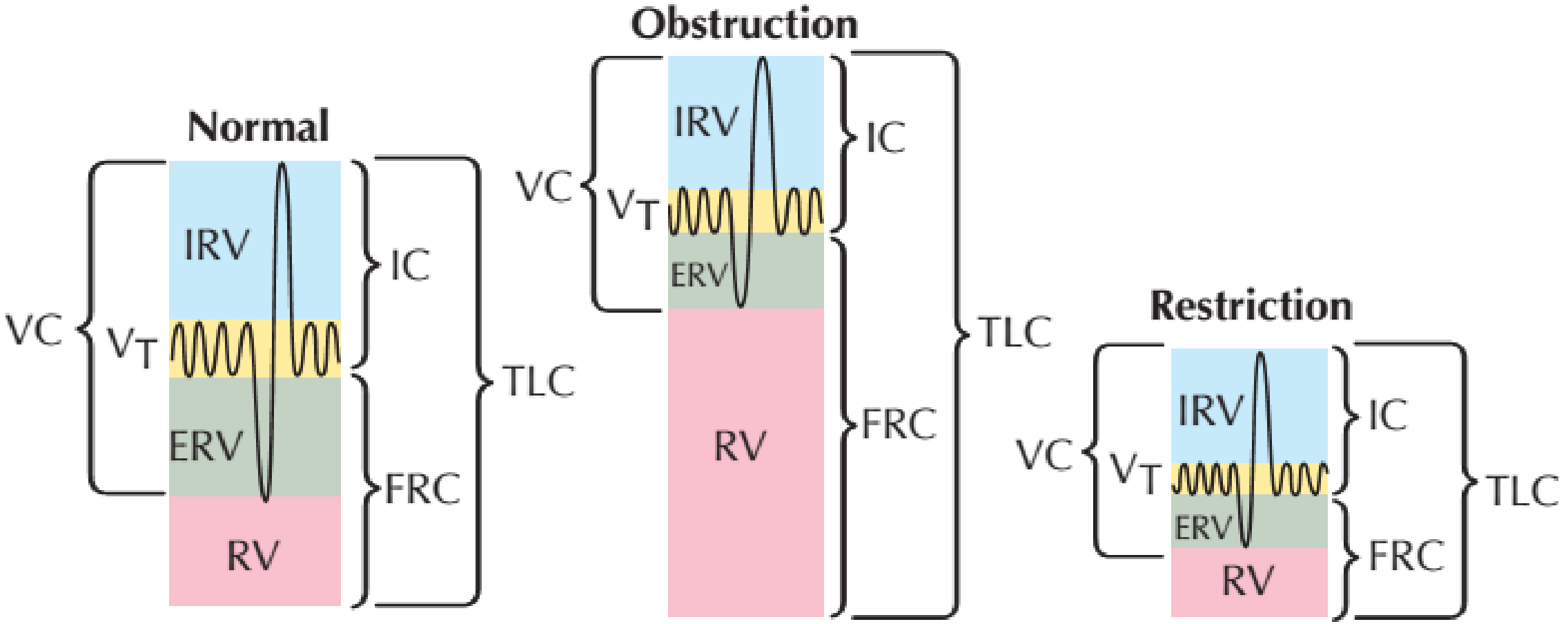
- FEV1
- FVC

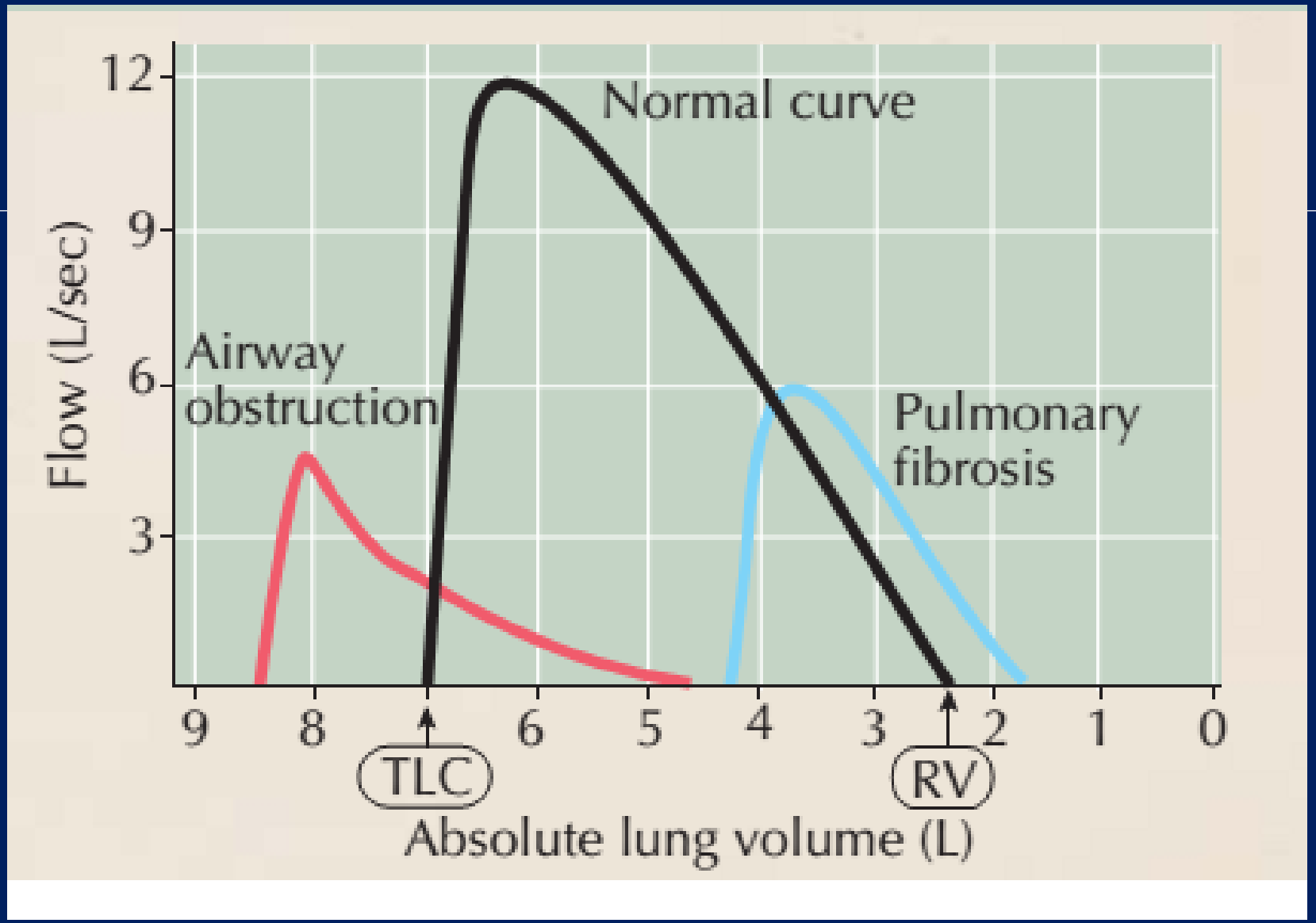
- FEV1/FVC ratio is usually normal or increased

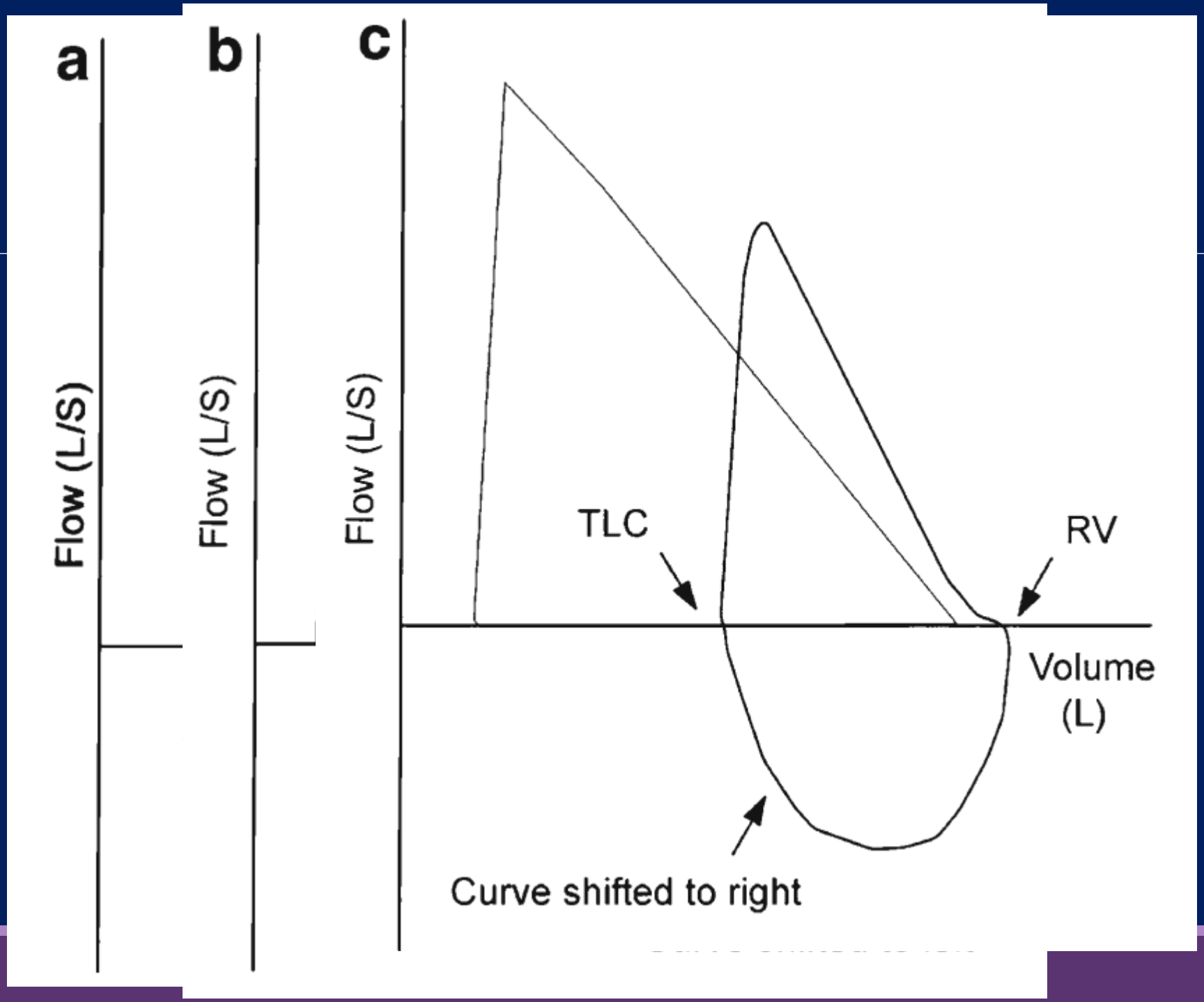

FORCED EXPIRATORY VITAL CAPACITY MANEUVER
Patient inspires maximally to total lung capacity, then exhales into spirometer as forcefully, as rapidly, and as completely as possible
F. Netter M.D.


Inspiratory reserve volume
Inspiratory capacity
Tidal volume
Total lung capacity
Expiratory reserve volume
Inspiratory vital capacity
Residual volume
Functional residual capacity

Interpretation




12
9
6
3
Flow (L/sec)
Normal curve
Airway
obstruction
Pulmonary
fibrosis
9
8
6
5
4
3
2
1
0
TLC
RV
Absolute lung volume (L)

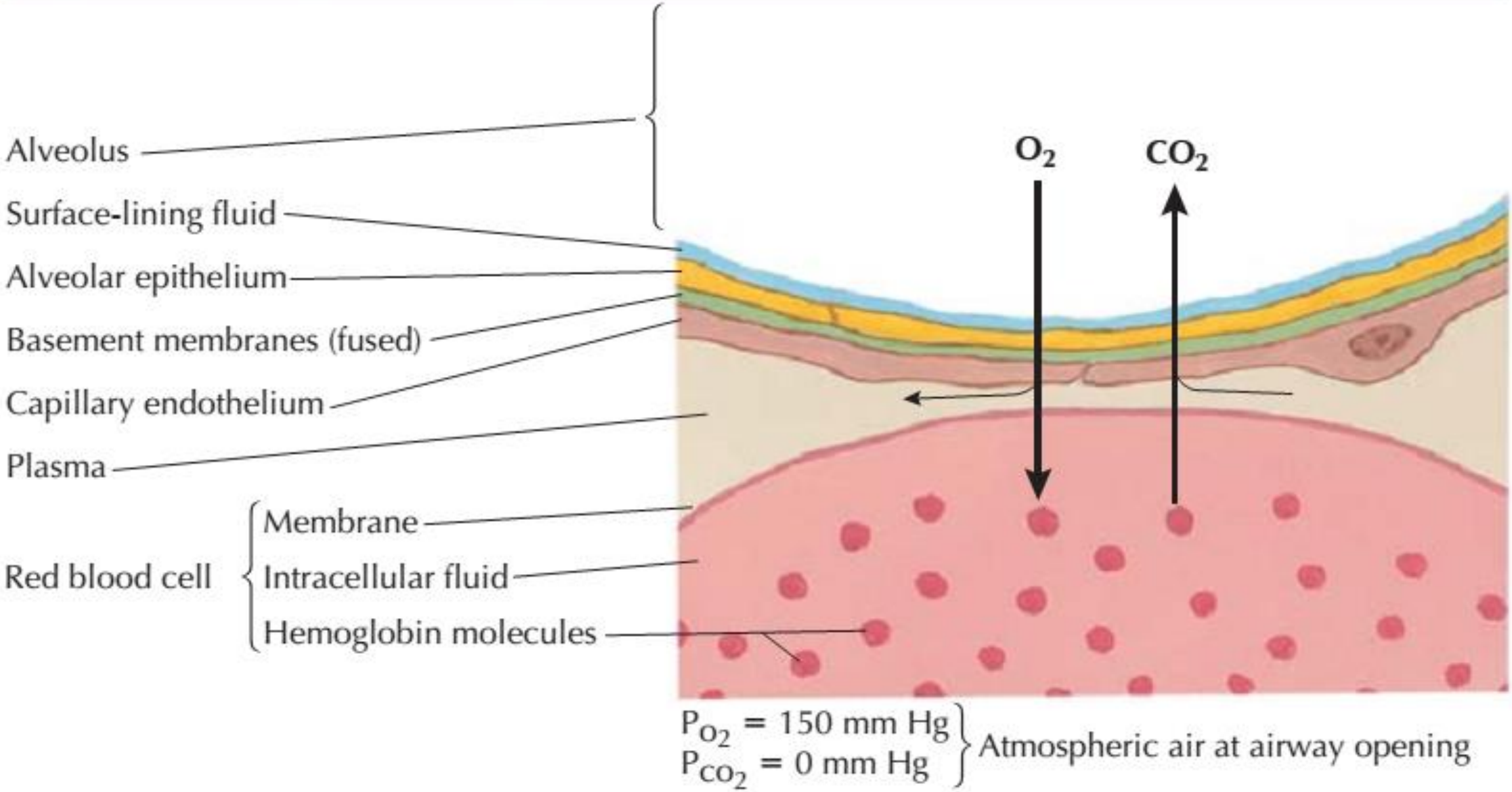

a
b
c
Flow (L/S)
Flow (L/S)
Flow (L/S)
TLC
RV
Volume
(L)
Curve shifted to right

Diffusing Capacity (DlCO)

- ↓ diffusing capacity of the lung for carbon monoxide

- common but nonspecific finding in most ILDs
- effacement of the alveolar capillary units

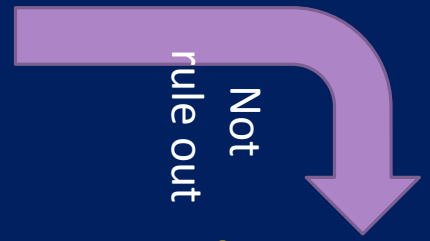
Pathways of O_2 and CO_2 diffuse



- ACCUMULATION OF FBROBLASTS
- TIS THICKENED INTERSTITIUM
- POOR OXYGENATION WITH EXERCISE,
- INCREASED LUNG STIffNESS EXHIBITED
- DECREASED COMPLIANCE,
- SMALL LUNG VOLUMES,
- INCREASED WORK OF BREATHING

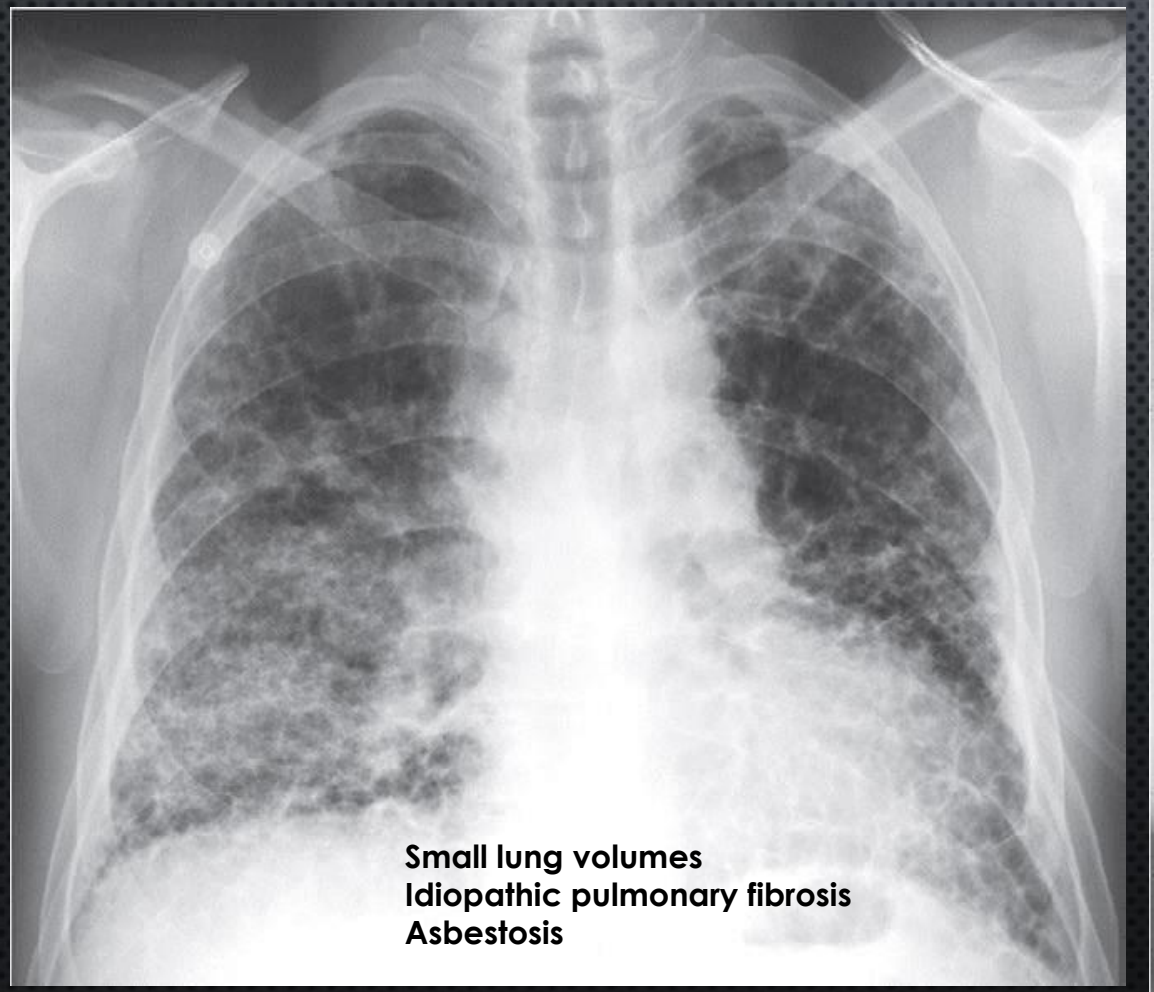
Arterial Blood Gas

- Resting ABG may be normal

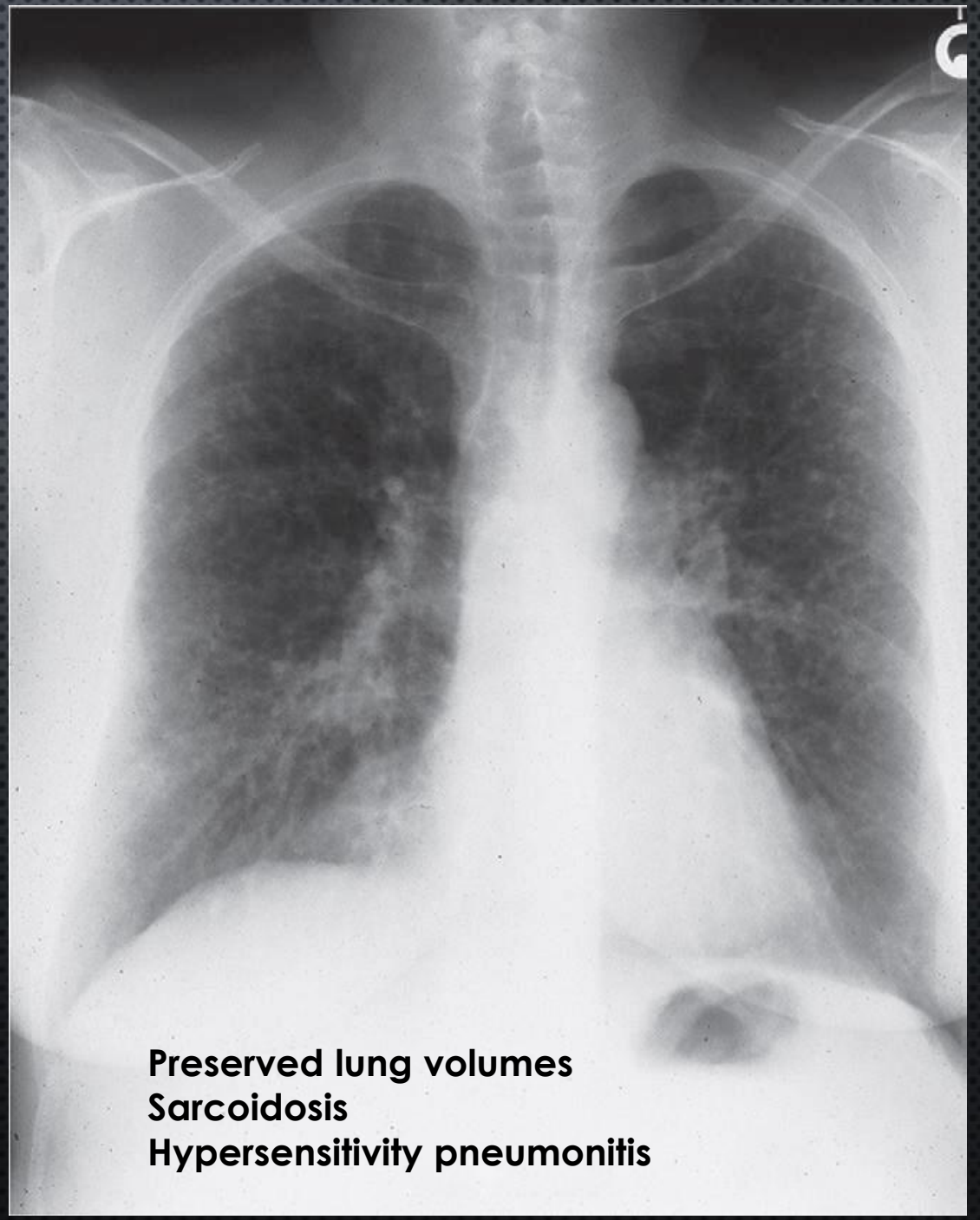


- significant hypoxemia during **exercise or sleep**
- hypoxemia & respiratory alkalosis

- Carbon dioxide (CO_2) retention is rare
- usually a manifestation of end-stage disease



Small lung volumes
Idiopathic pulmonary fibrosis
Asbestosis



Preserved lung volumes
Sarcoidosis
Hypersensitivity pneumonitis

MIXED PATERNS

- **LYMPHANGIOLEIOMYOMATOSIS**
  - SMALL AIRWAYS ARE NARROWED BY THE PROLIFERATION OF SURROUNDING ABNORMAL SMOOTH MUSCLE–LIKE CELLS.
  - INCREASED AIRWAY RESISTANCE AND AIRFLOW OBSTRUCTION.
- **SARCOIDOSIS**
  - ENDOBRONCHIAL DISEASE WITH DIRECT NARROWING OF THE AIRWAYS CAN OCCUR IN LEADING TO SIMILAR EFFECTS

DIAGNOSIS

- **CLINICAL AND IMAGING DATA ARE INSUFCIENTLY SPECIFC**
- **LUNG BIOPSY**
  - SURGICAL LUNG BIOPSY, A THORACOSCOPIC APPROACH
  - TBLB USEFUL FOR
    - SARCOIDOSIS
    - COP
    - HP

MANAGEMENT OF ILD

- DEPENDS ON THE UNDERLYING CAUSE

- EXPOSURE AVOIDANCE FOR HP, SMOKING-RELATED ILD, AND DRUG-INDUCED ILD.
- IMMUNOSUPPRESSANTS
- SUPPLEMENTAL OXYGEN AND PULMONARY REHABILITATION
- LUNG TRANSPLANTATION

Idiopathic Pulmonary Fibrosis

Idiopathic Pulmonary Fibrosis

- chronic, progressive fibrosing interstitial pneumonia
- un-known cause
- occurring primarily in older adults
- Limited to the lungs
- progressive worsening of dyspnea and lung function
- associated with a poor prognosis

Idiopathic Pulmonary Fibrosis

- 25% to 30% of ILDs
- **clinical, radiographic, physiologic, and pathologic**
  - **diagnosis of exclusion**

- prevalence 0.8 to 65/100,000
- Incidence 0.4 to 27/100,000

- increase markedly with age

Clinical Features
IPF

- middle age **50 and 70** years of age
- insidious onset of exertional breathlessness
- nonproductive cough
- Constitutional symptoms are uncommon
  - weight loss, fever, fatigue, myalgias, or arthralgia
- symptoms for months to years before definitive evaluation
  - 12 to 18 months

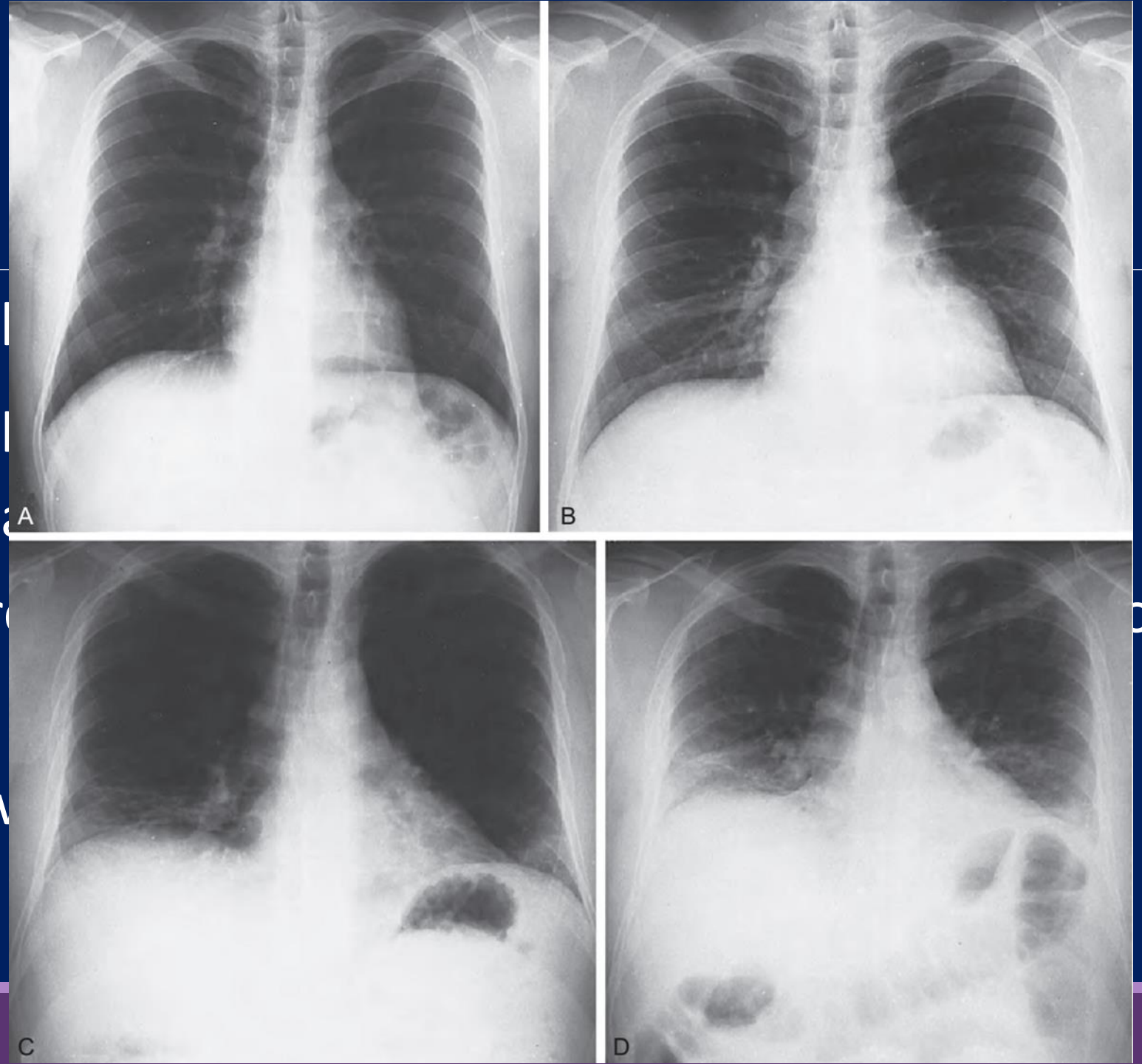
physical examination

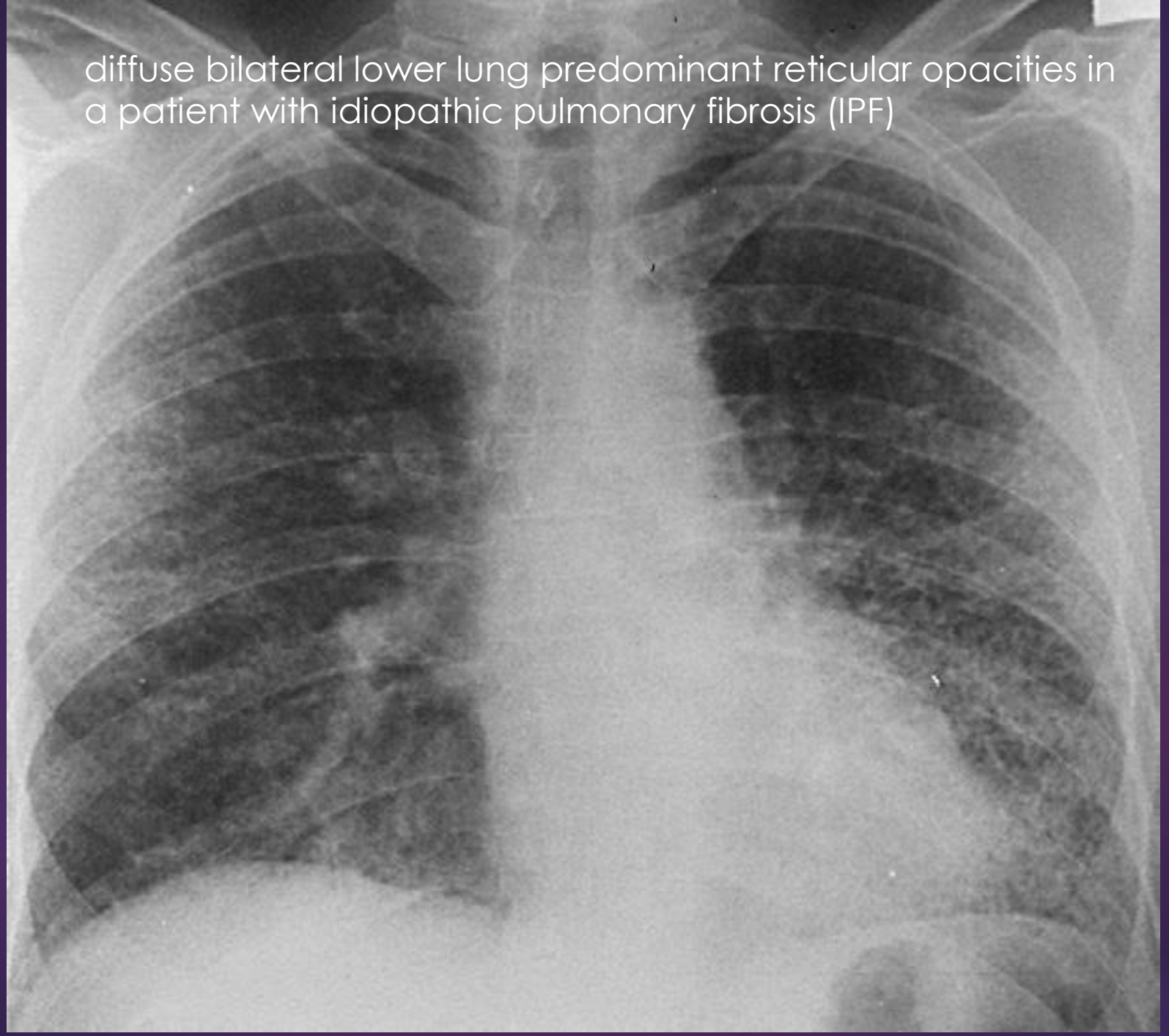
- Bibasilar late inspiratory fine crackles (Velcro crackles)
- Clubbing of the fingers is seen in 40% to 75% late
- Cardiac examination is usually normal except in the middle or late
- Findings of pulmonary hypertension
  - (e.g., augmented P2, right-sided lift, tricuspid regurgitation, and S3 gallop)
- Corpulmonale
- Cyanosis late manifestation
- Spontaneous pneumothorax or pneumomediastinum is rare

Blood and Serologic Studies

- ESR ↑
- low-level ANA titer positivity (≥40 and <1 : 320)
- ↑ RF (>60 IU/mL)
- CBC diff counts are usually normal

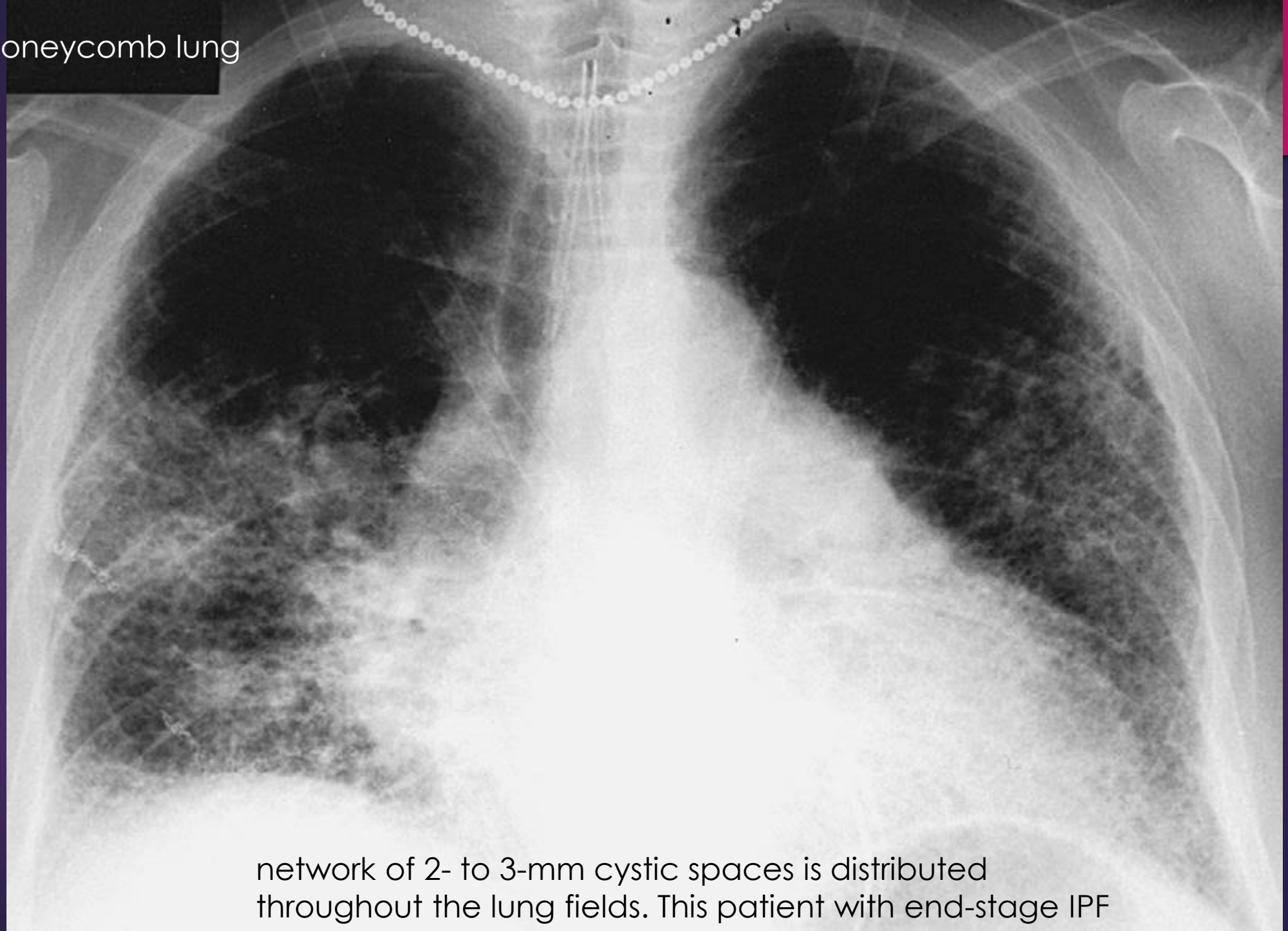
- peripheral
- netlike app
- predomina
- A coarse r ombed areas
- correlate v



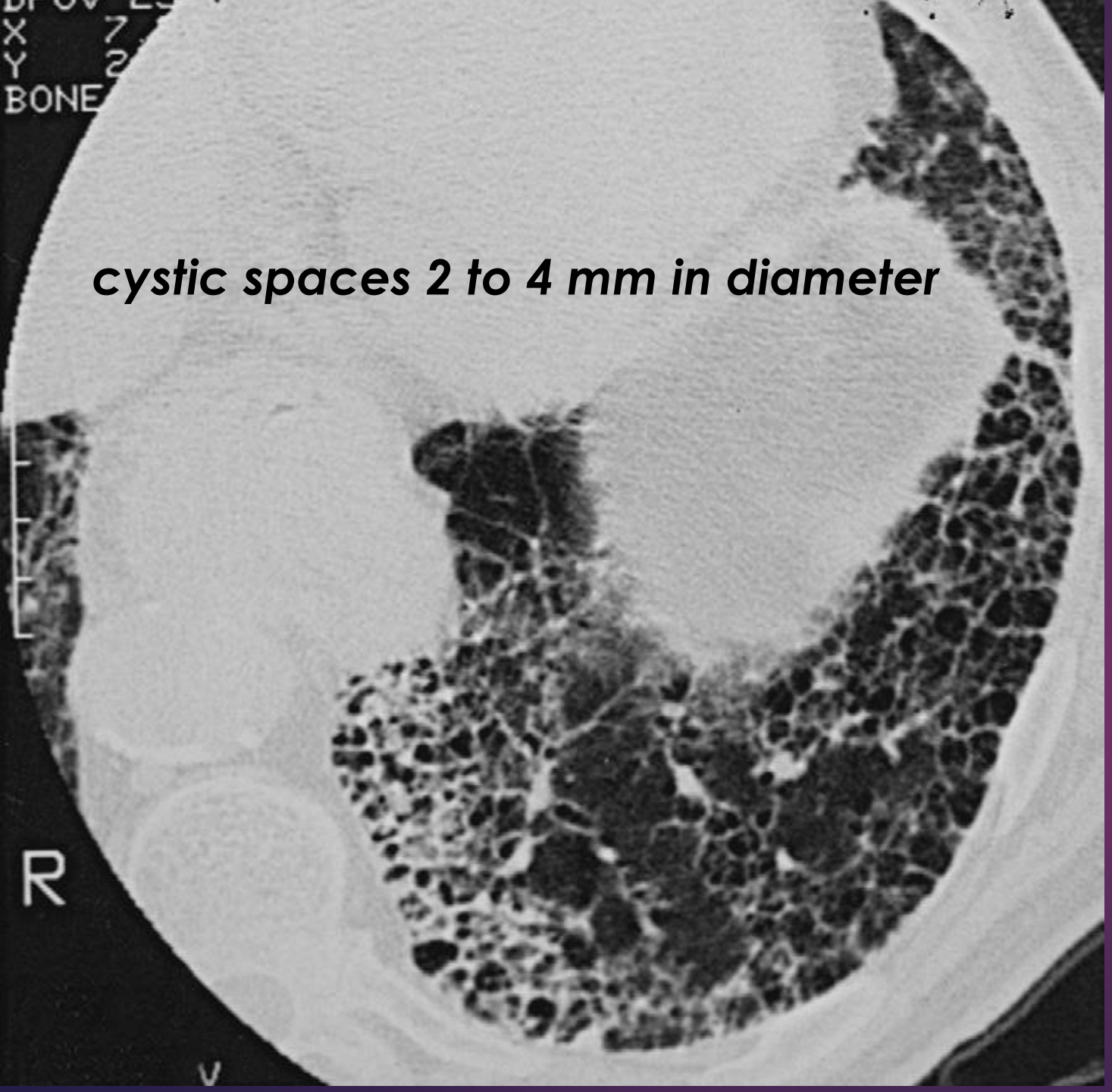


diffuse bilateral lower lung predominant reticular opacities in a patient with idiopathic pulmonary fibrosis (IPF)

honeycomb lung



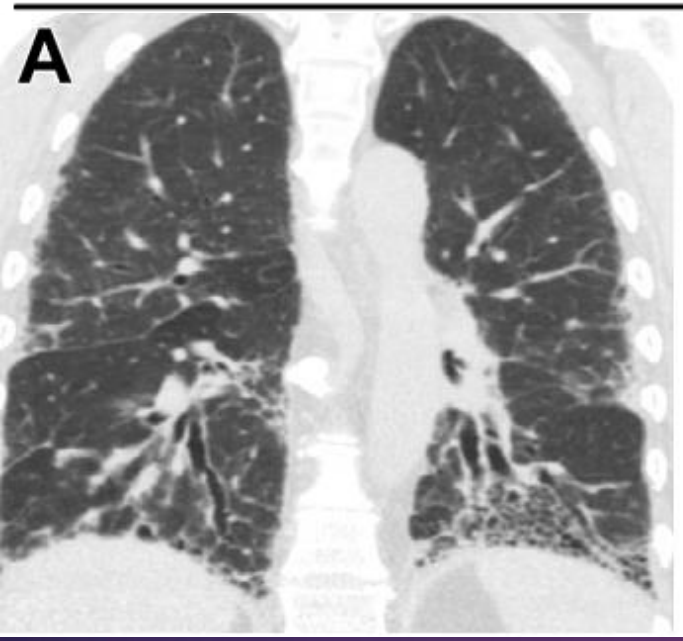
network of 2- to 3-mm cystic spaces is distributed throughout the lung fields. This patient with end-stage IPF

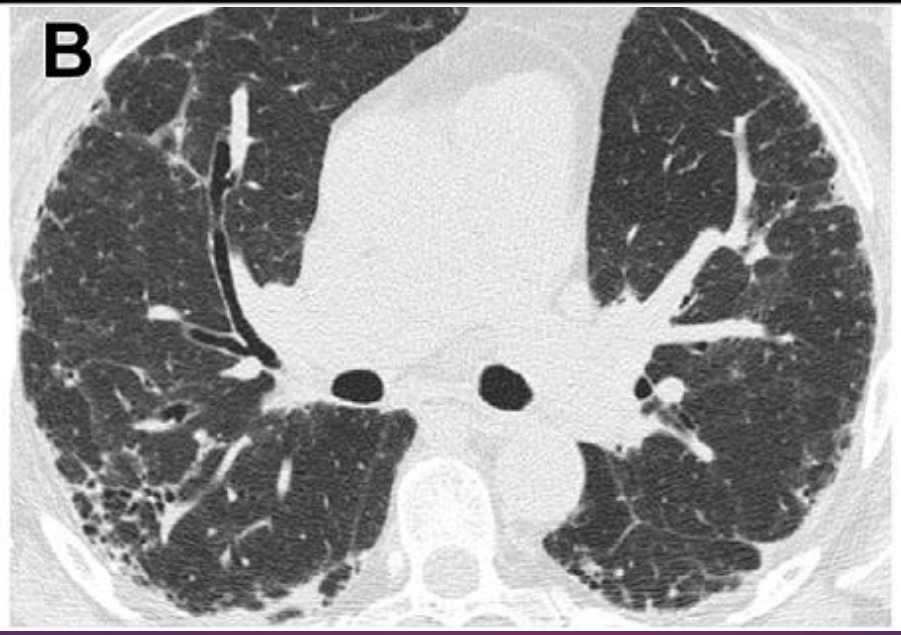


High-resolution CT image of advanced IPF shows extensive honeycomb changes

HRCT scan

	Distribution	Imaging Features
Usual interstitial pneumonia	Basal, peripheral predominant May be asymmetric and patchy	Reticulation, traction bronchiectasis/ bronchiolectasis Honeycombing





HRCT

- If honeycombing is absent on HRCT atypical features such as
  - ground-glass infiltrates
  - lymphadenopathy,
  - nodules,
  - air trapping

- lung biopsy may be needed

Pulmonary function tests

- restrictive pattern
- reduced DlCO
- arterial hypoxemia
  - exaggerated or elicited by exercise

Diagnosis

- Other potential causes of ILD, such as
  - connective tissue disease
  - hypersensitivity pneumonitis
  - Asbestosis

must be ruled out by

- history, examination, & selected laboratory testing

Treatment

- ***No effective therapy for IPF***
  - Thalidomide appears to improve cough
  - GERD therapy
  - Antifbrotic drug: pirfenidone
  - Lung transplantation

- Prednisone
- Azathioprine
- N-acetylcysteine (NAC)
- warfarin

increase the risks of hospitalization and death

GRANULOMATOUS DISORDERS INTERSTITIAL LUNG DISEASES WITH GRANULOMA FORMATION

Interstitial Lung Diseases with Granuloma Formation

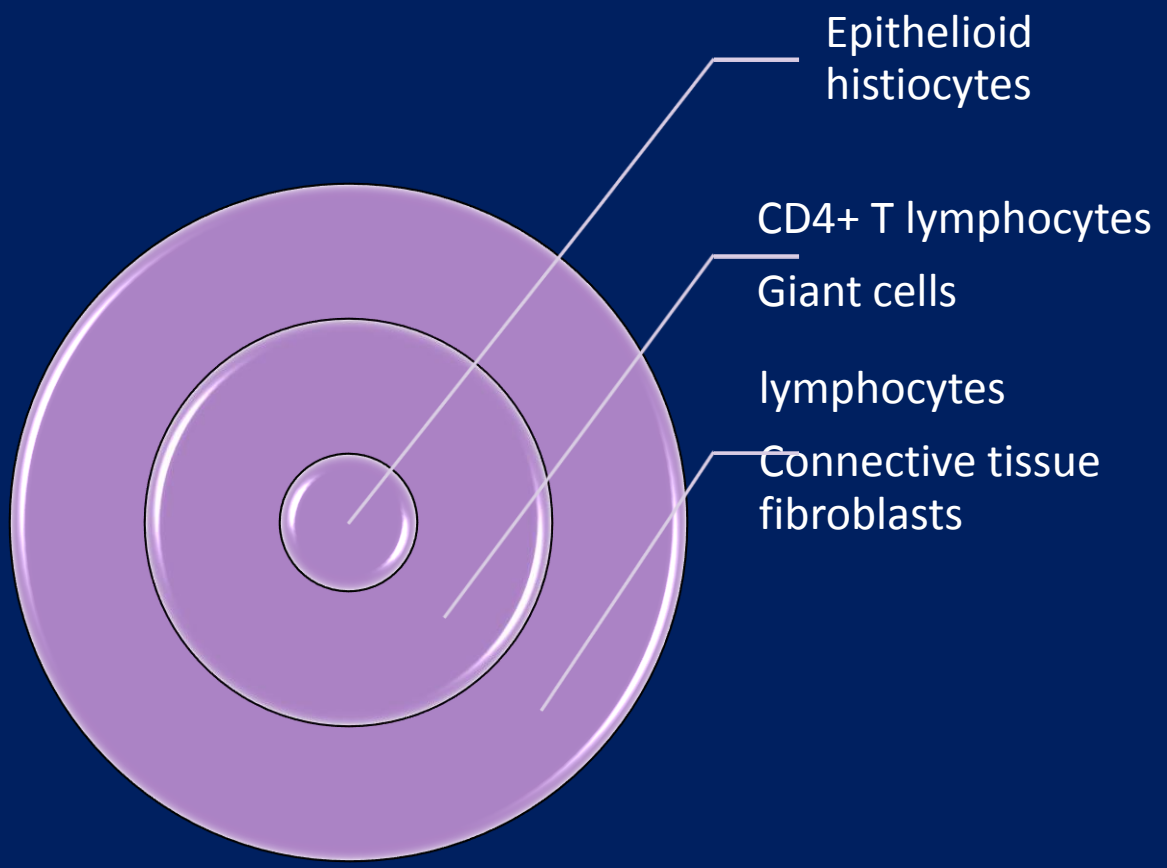
- granulomatosis with polyangiitis,
- HP
- chronic beryllium disease

- **sarcoidosis is the most common**

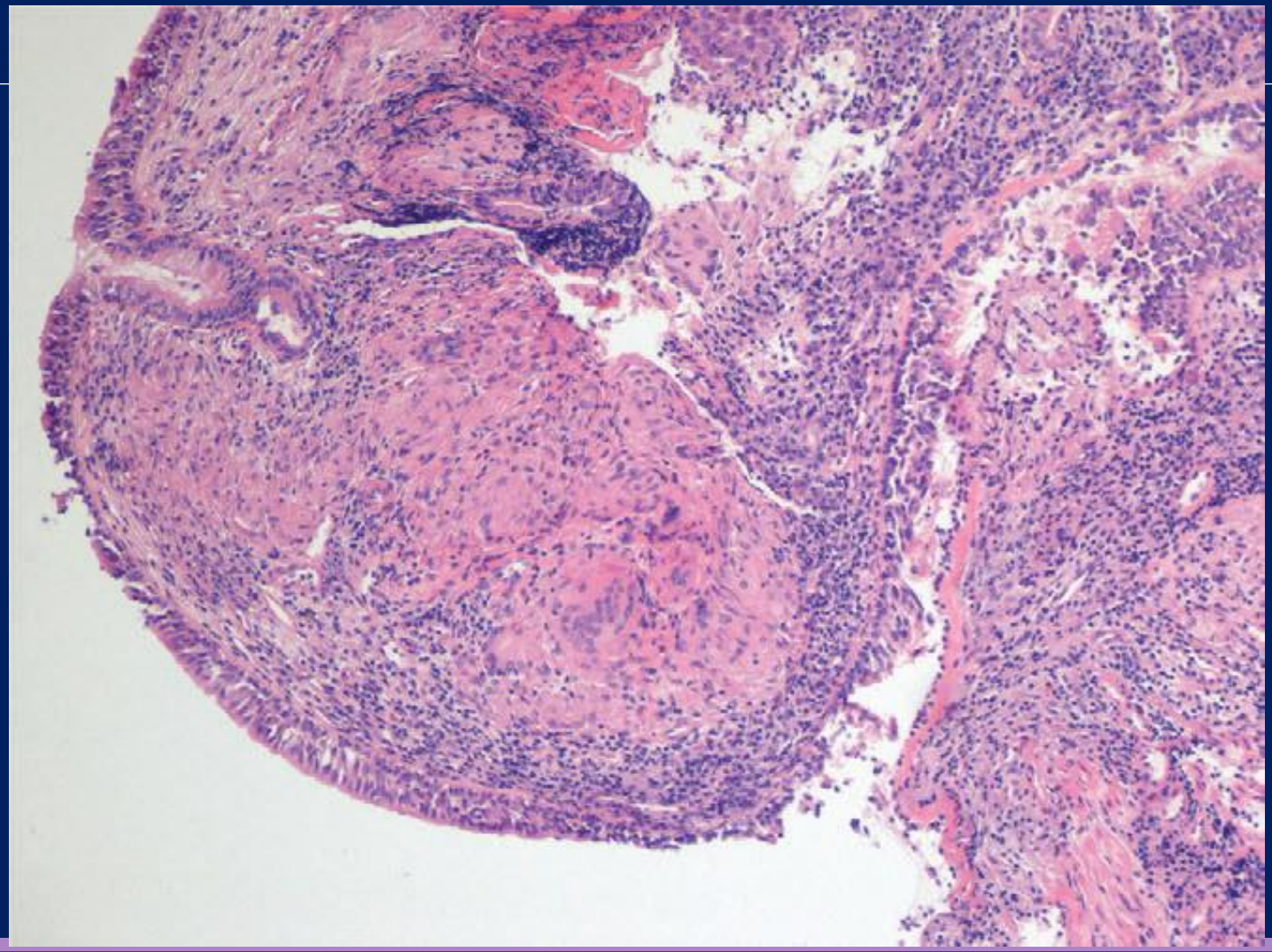
Sarcoidosis
Defnition and Epidemiology

- multisystem granulomatous disorder of unknown cause
- lungs and thoracic lymph nodes
- Prevalence of 1 to 40 cases per 100,000 people worldwide
- sarcoidosis may be asymptomatic
- typically occurs in individuals between 10 and 40 years old

Noncaseating granulomas Pathology Sarcoidosis



Subepithelial noncaseating granuloma



Sarcoidosis commonly involved

- Upper respiratory system
- Lymph nodes
- Skin
- Eyes

Sarcoidosis
Virtually any other organ may be affected

- Liver
- bone marrow
- Spleen
- musculoskeletal system
- Heart
- salivary glands
- nervous system

Sarcoidosis

- The granulomas may be clinically silent
- cause of these lesions is unknown
  - inhaled antigens ?
    - Mycobacteria and Propionibacterium ?
    - Environmental substances ?
- This inflammation may be self-limited

Sarcoidosis

- ***Abnormal immune function***
- Cutaneous anergy
- exhibited in lung by an ↑ CD4+/CD8+ T lymphocytes
- ↑ pro-inflammatory cytokines
  - Interferon γ
  - Interleukin 12
  - TNF α
- immunomodulatory therapy, especially with INF α
- immune reconstitution syndrome

Clinical Presentation acute

- incidentally on routine CXR of asymptomatic individuals
- ***Löfgren syndrome***
  - Erythema nodosum
  - Fever
  - Arthritis
  - Hilar adenopathy
- ***Uveoparotid fever (i.e., Heerfordt's syndrome)***
  - Uveitis
  - Parotitis
  - Facial nerve palsy
- beter outcomes than for other clinical presentations of sarcoidosis

Clinical Presentation vague and chronic

- low-grade fevers
- Fatigue
- night sweats
- joint pains

Clinical Presentation
Respiratory manifestations

- ***one third to one half of patients***
- shortness of breath
- Wheezing
- dry cough
- chest pain

Clinical Presentation
Skin manifestations

- erythema nodosum
- Plaques
- Nodules
- lupus pernio
  - violaceous, disfguring, nodular lesion of the nose and cheeks

Erythema nodosum

Clinical Presentation
Ocular symptoms

- Common
- onset of uveitis may eventually lead to the diagnosis
- granulomatous extraocular organ involvement ?

Clinical Presentation Neurosarcoidosis

- cranial nerve palsies
- headache in the seting of lymphocytic meningitis

Clinical Presentation involve the heart

- Cardiomyopathy
- Arrhythmias and sudden cardiac death
  - conducting system by granulomatous infiltration
- Pulmonary hypertension
  - pulmonary fibrosis
  - Directly from granulomatous vasculitis

HILAR ADENOPATHY IN A PATIENT WITH SARCOIDOSIS

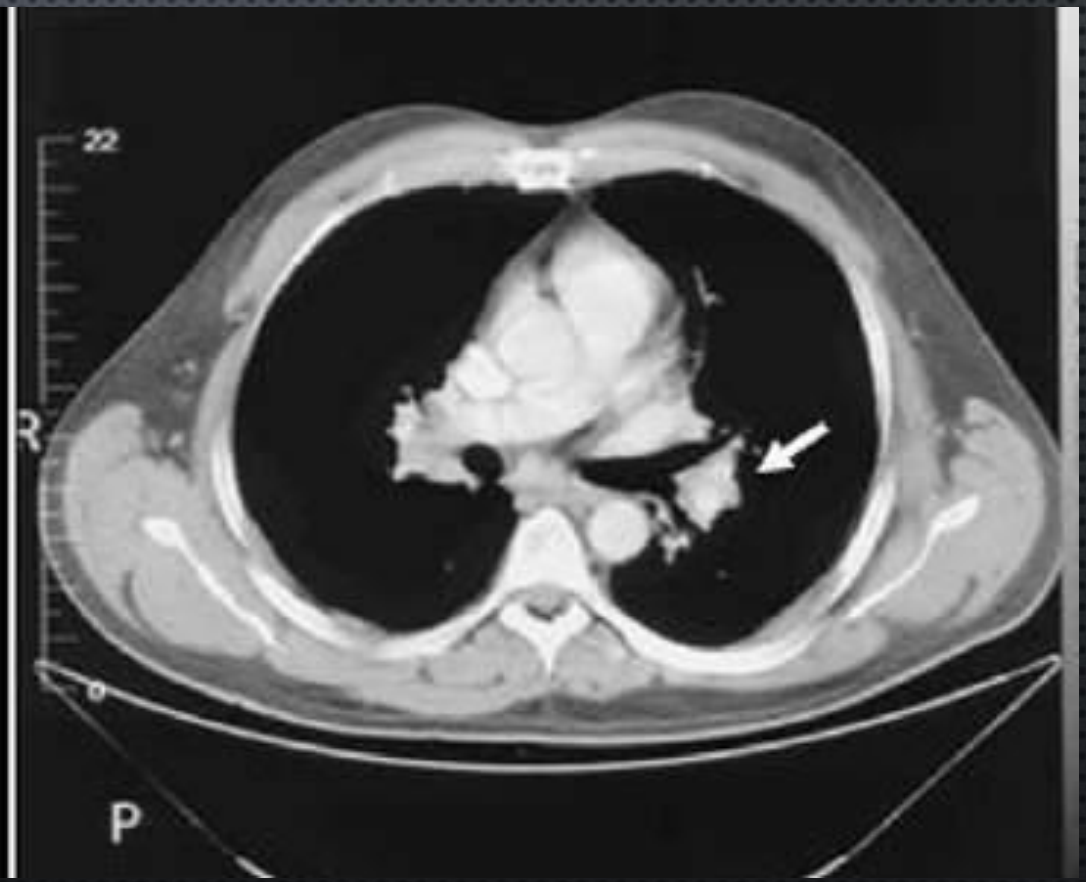
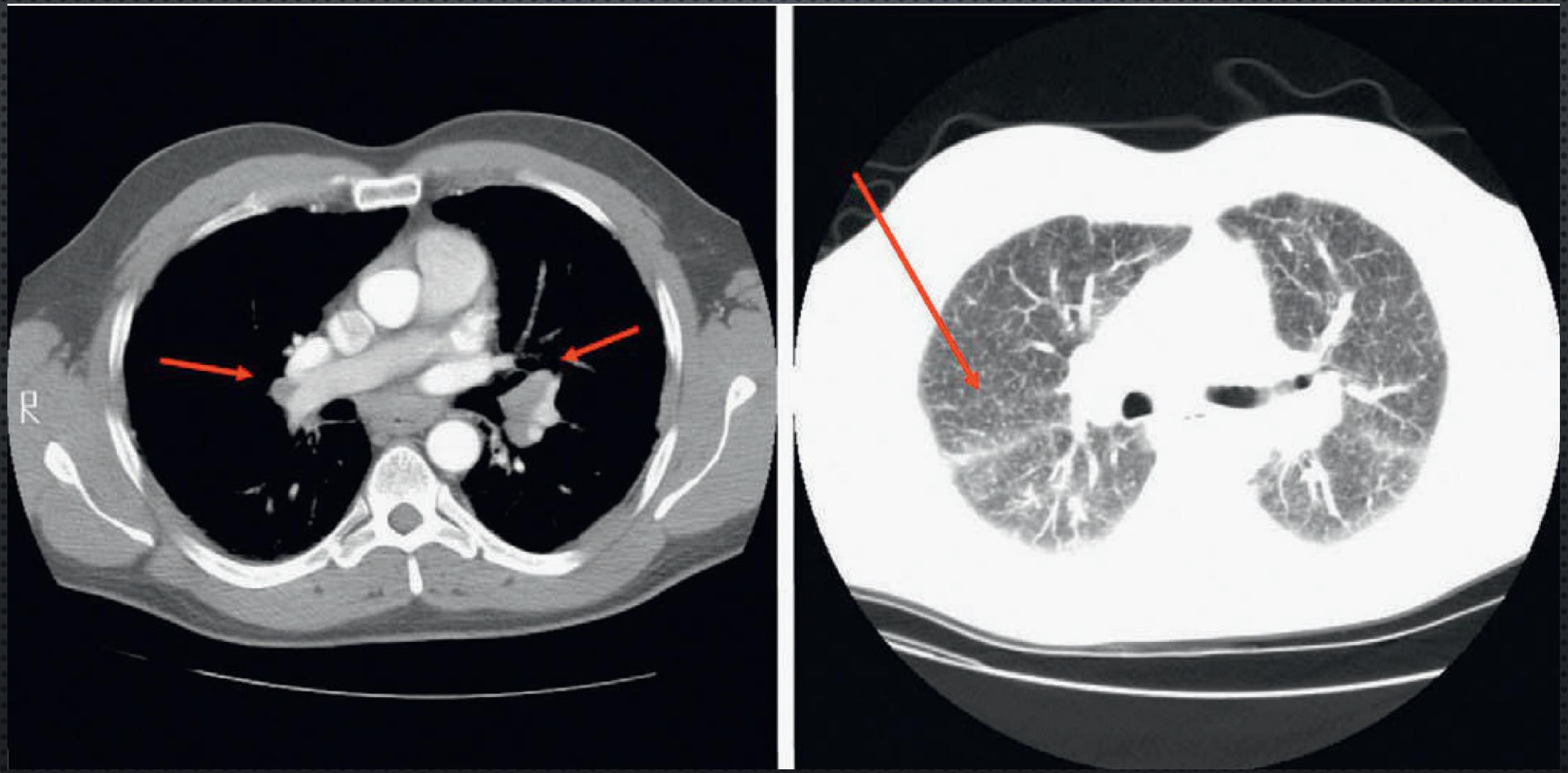


TABLE 17-2 RADIOGRAPHIC STAGING OF SARCOIDOSIS

STAGE	RADIOGRAPHIC FINDINGS
0	Normal radiograph
I	Adenopathy without parenchymal abnormality
II	Adenopathy and parenchymal disease
III	Parenchymal disease without lymphadenopathy
IV	End-stage fibrosis

Sarcoidosis with interstitial infltrates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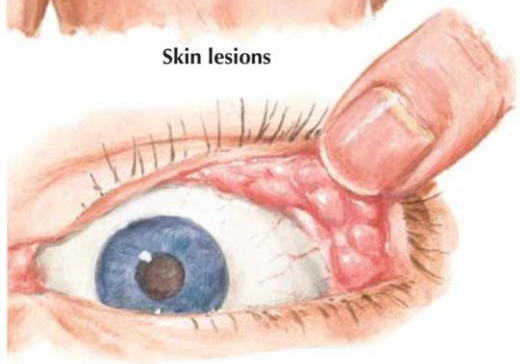
SARCOIDOSIS

- Pulmonary function tests show restriction or obstruction
- Liver involvement may cause mild elevation of AST & ALT
  - cirrhosis and liver failure rare
- Hypercalcemia and hypercalciuria
  - Kidney stones
- Elevated levels of ACE are common but are not specific

Diagnosis of sarcoidosis

- typical clinical, radiographic, and histologic picture
- diagnosis of exclusion
- Löfgren syndrome or uveoparotid fever may not require biopsy
- most patients require tissue biopsy of an affected organ
  - noncaseating granulomas
- ruling out other causes of granulomatous inflammation
  - mycobacterial infection
  - Necrotizing granulomas

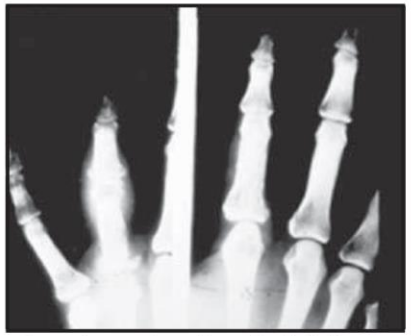
Skin lesions



Lacrimal gland involvement

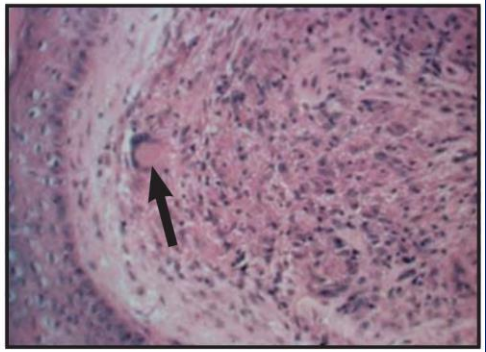
Bilateral parotid gland involvement

Paralysis caused by involvement of facial (VII) nerve



Bone destruction of terminal phalanges

Chest computed tomography scan



Biopsy of nodule. Reveals typical sarcoidal granuloma (dense infiltration with macrophages, epithelioid cells, and occasional multinucleated giant cells)

Diagnosis of sarcoidosis

- ***Bronchoscopy with TBLB*** are positive for 50% to 60%
  - hemorrhage and pneumothorax
- ***Endobronchial biopsies***
- ***TBNA*** of mediastinal and hilar lymph nodes
  - Endobronchial ultrasound guidance

Diagnosis of sarcoidosis

- ophthalmologic evaluation
- 24-hour collection of urine
- ECG & Holter monitoring
  - If cardiac sarcoidosis is suspected
    - MRI or PET scanning

Treatment

- ***Corticosteroids***
  - not cause symptoms or complications
  - spontaneous remission
- ***extrapulmonary organ involvement***
- ***progressive pulmonary symptoms***
- 20 to 40 mg per day may be initiated
- steroid-sparing agents
  - methotrexate
  - Infliximab, an anti-TNF agent

Treatment

- erythema nodosum in the seting of Löfgren syndrome
  - nonsteroidal anti-inflamatory
- Other skin involvement
  - hydroxychloroquine or topical corticosteroids
- lupus pernio
  - infliximab
- anti-TNF agents
  - extrapulmonary disease not responding to conventional therapy

Treatment

- Anterior uveitis
  - topical steroids
- Other eye involvement
  - systemic corticosteroids
- cardiac sarcoidosis
  - systemic corticosteroids
- Conduction system disease and arrhythmias
  - placement of pacemakers or automatic ICD
- Neurosarcoidosis and hypercalcemia
  - systemic steroid

Prognosis

- Spontaneous remission is common
- death and disability occur rarely
- acute sarcoidosis syndromes tend to remit and not recur
- 1/3 patients with sarcoidosis have chronic, progressive
- some patients develop pulmonary fibrosis or other EOD

Summary

- Presents in many ways
- Usually lungs
- Any organ